FDA Briefing Document

Arthritis Advisory Committee Meeting

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BLA 761042
GP2015, a proposed biosimilar to Enbrel (etanercept)

Sandoz

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring the 351(k) BLA for GP2015 with the Applicant's proposed indications to this Advisory Committee to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Table of Contents

1 INTRODUCTION 8
2 BACKGROUND 9
3 EXECUTIVE SUMMARY 11
4 DRAFT POINTS TO CONSIDER 13
5 RELEVANT REGULATORY HISTORY 14
6 CMC 14
7 PHARMACOLOGY/TOXICOLOGY 40
8 CLINICAL PHARMACOLOGY 41
9 CLINICAL OUTCOMES 50
10 CONSIDERATIONS FOR EXTRAPOLATION OF BIOSIMILARITY 65
11 SUMMARY 67

List of Tables (all tables are from FDA sources unless noted)

Table 1: Quality Attributes and Methods Used to Evaluate Analytical Similarity of GP2015, US-licensed Enbrel, and EU-approved Enbrel..20
Table 2: Descriptive Statistics for the T7 Peptide Data of GPP2015, US-licensed Enbrel, and EU-approved Enbrel.....23
Table 3: Descriptive Statistics for the RPC "Post-Peak" Data of GPP2015, US-licensed Enbrel, and EU-approved Enbrel.....25
Table 4: Descriptive Statistics for the TNF-α Binding Data 25
Table 5: Equivalence Testing Results for the TNF-α Binding.....26
Table 6: Descriptive Statistics for the *in vitro* TNF-α Neutralization RGA Data of GP2015, US-licensed Enbrel, and EU-approved Enbrel .27
Table 7: Equivalence Testing Results for the *in vitro* TNF-α Neutralization RGA of GP2015, US-licensed Enbrel, and EU-approved Enbrel 27
Table 8: Descriptive Statistics for the *in vitro* TNF-α Neutralization RGA Data of GP2015, US-licensed Enbrel, and EU-approved Enbrel Based on the Computed Potency Model.....30
Table 9: Equivalence Testing Results for the *in vitro* TNF-α Neutralization RGA of GP2015, US-licensed Enbrel, and EU-approved Enbrel Based on the Computed Potency Model.....30
Table 10: Descriptive Statistics for the *in vitro* TNF-α Neutralization Apoptosis Data of GP2015, US-licensed Enbrel, and EU-approved Enbrel 32
Table 11: Descriptive Statistics for the *in vitro* TNF-β Neutralization RGA Data of GP2015, US-licensed Enbrel, and EU-approved Enbrel .33
Table 12. Key Design Features of GP2015 Clinical Studies.....42
Table 13. Statistical Analysis of the PK Parameters of GP2015 and US-Licensed Enbrel in Study 102 44
Table 14. Statistical Analysis of the PK Parameters of GP2015 and EU-approved Enbrel in Study 101.....45
Table 15. Statistical Analysis of the PK Parameters of GP2015 and EU-approved Enbrel in Study 104.....46
Table 16. Statistical Analysis of the PK Parameters of EU-approved Enbrel and US-Licensed Enbrel in Report 105 48
Table 17. Patient Disposition in Treatment Period 1 (Week 1-12), Study 302 54
Table 18. Exact Confidence Intervals for the Risk Difference of PASI 75 Response Rates, Study 302 55

Table 19. Analyses Using Various Prior Therapy Variable Definitions (FAS), Study 302 55
Table 20. Summary of Adverse Events in Treatment Periods 1 and 2 Through Week 30, Study 302 58
Table 21. Serious Adverse Events in Treatment Periods 1 and 2 Through Week 30, Study 302 59
Table 22. TEAEs Leading to Study Drug Discontinuation in Treatment Periods 1 and 2 through Week 30, Study 302 60
Table 23. Adverse Events of Special Interest in Treatment Periods 1 and 2 Through Week 30, Study 302 62
Table 24. Anti-drug Antibody Response in Treatment Periods 1 and 2 64

List of Figures (all figures are from FDA sources unless noted)

Figure 1: TNF-α: A "Master Cytokine" 16
Figure 2: Etanercept and Anti-TNF mAbs Binding to mTNF 17
Figure 3: Representation of TNFR Intrachain Disulfide Bonds 22
Figure 4: Incorrect Interchain Disulfide Bonds in GP2015 23
Figure 5: RPC-Chromatogram of GP2015 24
Figure 6: Comparative Potency (Competitive SPR) of GP2015, US-licensed Enbrel, and EU-approved Enbrel to Human TNF-α 26
Figure 7: TNF-α RGA of GP2015, US-licensed Enbrel, and EU-approved Enbrel 28
Figure 8: Structure-Function Relationship Between the T7 Peptide and Bioactivity 29
Figure 9: TNF-α RGA of GP2015, US-licensed Enbrel, and EU-approved Enbrel Based on the Computed Potency Model 30
Figure 10: TNF-α Neutralization by Apoptosis of GP2015, US-licensed Enbrel, and EU-approved Enbrel 31
Figure 11: TNF-β Neutralization RGA of GP2015, US-licensed Enbrel, and EU-approved Enbrel 32
Figure 12: The Role of Fc in the Anti-TNF-α Class Mechanism(s) of Action 34
Figure 13: Comparison of Different TNF antagonists in the ADCC Assay 35
Figure 14: ADCC activity of GP2015, US-licensed Enbrel, and EU-Approved Enbrel of LPS Primary Human Monocytes by an NK Cell Line 35
Figure 15: HDX Heat Map for GP2015, US-licensed Enbrel, and EU-approved Enbrel 37
Figure 16: 1D 1H NMR spectrum (overlay) of GP2015 US-licensed Enbrel 38
Figure 17. Geometric Mean Serum Concentration-time Profiles of GP2015 (red, N=54) and US-licensed Enbrel (blue, N=54) from Study 102 45
Figure 18. Geometric Mean Serum Concentration-Time Profiles of GP2015 (red, N=50) and EU-approved Enbrel (green, N=50) from Study 101 46
Figure 19. Geometric Mean Serum Concentration-time Profiles of GP2015 (red, N=54) and EU-approved Enbrel (green, N=54) from Study 104 47

Figure 20. Geometric Mean Serum Concentration-time Profiles of EU-approved Enbrel (green, N=50) and US-licensed Enbrel (blue, N=54) from Report 105 48
Figure 21. Geometric Mean Trough Serum Concentration-time Profiles of GP2015 (red, N=72) and EU-approved Enbrel (green, N=75) from Study 302 49
Figure 22. Schemata of Study 302 Design 52

1 Introduction

Sandoz has submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for GP2015[1], a proposed biosimilar to Enbrel (etanercept). BLA # 103795 for Enbrel was initially licensed by FDA on November 2, 1998, and the BLA is currently held by Amgen, Inc. Sandoz is seeking licensure of GP2015 for the following indications for which US-licensed Enbrel is licensed:[2]

1) Rheumatoid Arthritis (RA):
   - Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis (in combination with methotrexate, MTX, or used alone);

2) Polyarticular Juvenile Idiopathic Arthritis (JIA):
   - Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients ages 2 and older;

3) Psoriatic Arthritis (PsA):
   - Reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis (in combination with MTX in patients who do not respond adequately to MTX alone);

4) Ankylosing Spondylitis(AS):
   - Reducing signs and symptoms in patients with active ankylosing spondylitis;

5) Plaque Psoriasis (PsO):
   - Treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

[1] In this document, FDA generally refers to Sandoz's proposed product by the Sandoz descriptor "GP2015." FDA has not yet designated a nonproprietary name for Sandoz's proposed biosimilar product that includes a distinguishing suffix (see Draft Guidance on Nonproprietary Naming of Biological Products).
[2] FDA-approved Enbrel labeling

2 Background

Introduction to Regulatory Pathway

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was passed as part of health reform (Affordable Care Act) that President Obama signed into law on March 23, 2010. The BPCI Act created an abbreviated licensure pathway for biological products shown to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product (the "reference product"). This abbreviated licensure pathway under section 351(k) of the PHS Act permits reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product-specific nonclinical and clinical data.

Section 351(k) of the PHS Act defines the terms "biosimilar" or "biosimilarity" to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." A 351(k) application must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

Development of a biosimilar product differs from development of a biological product intended for submission under section 351(a) of the PHS Act (i.e., a "stand-alone" marketing application). The goal of a "stand-alone" development program is to demonstrate the safety, purity and potency of the proposed product based on data derived from a full complement of clinical and nonclinical studies. The goal of a biosimilar development program is to demonstrate that the proposed product is biosimilar to the reference product. While both stand-alone and biosimilar product development programs generate analytical, nonclinical, and clinical data, the number and types of studies conducted will differ based on differing goals and the different statutory standards for licensure.

To support a demonstration of biosimilarity, FDA recommends that applicants use a stepwise approach to developing the data and information needed. At each step, the applicant should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product to the reference product and identify next steps to try to address that uncertainty. The underlying presumption of an abbreviated development program is that a molecule that is shown to be structurally and functionally highly similar to a reference product is anticipated to behave like the reference product

in the clinical setting(s). The stepwise approach should start with extensive structural and functional characterization of both the proposed biosimilar product and the reference product, as this analytical characterization serves as the foundation of a biosimilar development program. Based on these results, an assessment can be made regarding the analytical similarity of the proposed biosimilar product to the reference product and, once the applicant has established that the proposed biosimilar meets the analytical similarity prong of the biosimilarity standard, the amount of residual uncertainty remaining can be assessed with respect to both the structural/functional evaluation and the potential for clinically meaningful differences. Additional data, such as nonclinical and/or clinical data, can then be tailored to address these residual uncertainty(-ies).

The 'totality of the evidence' submitted by the applicant should be considered when evaluating whether an applicant has adequately demonstrated that a proposed product meets the statutory standard for biosimilarity to the reference product. Such evidence generally includes structural and functional characterization, animal study data, human PK and, if applicable, pharmacodynamics (PD) data, clinical immunogenicity data, and other clinical safety and effectiveness data.

The Reference Product

In general, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the reference product.[3] When an applicant's proposed biosimilar development program includes data generated using a non-US-licensed comparator to support a demonstration of biosimilarity to the US-licensed reference product, the applicant must provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the US-licensed reference product. As a scientific matter, the type of bridging data needed will always include data from analytical studies (e.g., structural and functional data) that directly compare all three products [i.e., the proposed biosimilar product, the reference product, and the non-US-licensed comparator product] and is likely to also include bridging clinical PK and/or PD study data for all three products.

[3] The BPCI Act defines the "reference product" as the single biological product licensed under section 351(a) of the PHS Act against which a proposed biosimilar product is evaluated in a 351(k) application (see section 351(i)(4) of the PHS Act).

3 Executive Summary

This is a 351(k) BLA submitted by Sandoz, Inc. for GP2015, a proposed biosimilar to Enbrel (etanercept). Sandoz is seeking licensure of GP2015 for the same indications previously approved for US-licensed Enbrel. The application consists of:

- Extensive analytical data intended to support (i) a demonstration that GP2015 and US-licensed Enbrel are highly similar, (ii) a demonstration that GP2015 can be manufactured in a well-controlled and consistent manner, leading to a product that is sufficient to meet appropriate quality standards and (iii) a justification of the relevance of comparative data generated using the European Union (EU)-approved Enbrel to support a demonstration of the biosimilarity of GP2015 to US-licensed Enbrel.

- Three single-dose pharmacokinetic (PK) studies (101 and 102, 104, and cross-study comparison Report 105) providing a comparison of GP2015, US-licensed Enbrel, and EU-approved Enbrel intended to (i) support PK similarity of GP2015 and US-licensed Enbrel and (ii) provide PK data to support the relevance of the comparative data generated using EU-approved Enbrel to support a demonstration of the biosimilarity of GP2015 to US-licensed Enbrel.

- A comparative clinical study (Study 302) between GP2015 and EU-approved Enbrel to support a demonstration of no clinically meaningful differences. This is a 52-week, randomized, double-blind, multicenter study conducted outside the US in 531 patients with moderate to severe, chronic plaque-type psoriasis (PsO), who were randomized 1:1 to GP2015 or EU-approved Enbrel at a dose of 50 mg twice weekly for 12 weeks (treatment period 1, TP1). Patients who completed the Week 12 visit and achieved at least a Psoriasis Area Severity Index (PASI) 50 response at that visit were re-randomized to either continue on their initial treatment or to undergo pre-defined switches between the two products from Week 12 to Week 30 (treatment period 2, TP2). This application includes an assessment of safety and immunogenicity in patients who completed TP2.

- A scientific justification for extrapolation of data to support biosimilarity in each of the non-studied indications for which Sandoz is seeking licensure, specifically rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS).

Sandoz submitted comparative analytical data on the GP2015 lots used in clinical studies intended to support a demonstration of biosimilarity (“clinical product lots”) and on the proposed commercial product. Based on our review of the data provided, Sandoz’s comparative analytical data for GP2015 demonstrates that it is highly similar to US-licensed Enbrel notwithstanding minor differences in clinically inactive components.

Sandoz used a non-US-licensed comparator (European Union (EU)-approved Enbrel) in some studies intended to support a demonstration of biosimilarity to US-licensed Enbrel. Accordingly, Sandoz provided scientific justification for the relevance of that data by establishing an adequate scientific bridge between EU-approved Enbrel, US-licensed Enbrel, and GP2015. Review of an extensive battery of test results provided by Sandoz confirmed adequacy of the scientific bridge and hence the the relevance of comparative clinical and non-clinical data with EU-approved Enbrel to support a demonstration of biosimilarity to US-licensed Enbrel.

The results of the clinical development program indicate that Sandoz's data support the demonstration of "no clinically meaningful differences" between GP2015 and the US-Enbrel in terms of safety, purity, and potency in the indications studied. Specifically, the results from the comparative clinical efficacy, safety, and PK studies, adequately support the determination that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel. Further, the single transition from EU-approved Enbrel to GP2015 during treatment period 2 in Study 302 did not result in a different safety or immunogenicity profile. This would support the safety of the clinical scenario where non-treatment naïve patients undergo a single transition to GP2015.

In considering the totality of the evidence, the data submitted by Sandoz show that GP2015 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel in terms of the safety, purity, and potency of the product to support the demonstration that GP2015 is biosimilar to the US-licensed Enbrel in the studied indication of PsO.

The Applicant has also provided an extensive data package to address the scientific considerations for extrapolation of data to support biosimilarity to other conditions of use and potential licensure of GP2015 for each of the indications for which US-licensed Enbrel is currently licensed and for which GP2015 is eligible for licensure.

4 Draft Points to Consider

Discussion Point 1:
Does the Committee agree that GP2015 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components?

Discussion Point 2:
Does the Committee agree that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel in the studied condition of use (PsO)?

Discussion Point 3:
Does the Committee agree that there is sufficient scientific justification to extrapolate data from the comparative clinical study of GP2015 in PsO to support a demonstration of biosimilarity of GP2015 for the following additional indications for which US-licensed Enbrel is licensed (RA, JIA, PsA, and AS)? If not, please state the specific concerns and what additional information would be needed to support extrapolation. Please discuss by indication if relevant.

Voting Point 1:
Does the Committee agree that based on the totality of the evidence, GP2015 should receive licensure as a biosimilar product to US-licensed Enbrel for each of the following indications for which US-licensed Enbrel is currently licensed and GP2015 is eligible for licensure (RA, JIA, AS, PsA, PsO)?

5 Relevant Regulatory History

The development of GP2015 was done outside the US. The first interaction with the FDA about the GP2015 development program occurred at a Biosimilar Biological Product Development (BPD) Type 2 meeting held on 9 July 2012. A second BPD Type 2 meeting was held on 19 December 2012. Additional interactions occurred to discuss the initial Pediatric Study Plan (iPSP). At the BPD Type 2 meetings, FDA provided general guidance on the proposed comparative clinical study design including primary endpoint and similarity margin to support a filing of the 351(k) BLA. The FDA also provided product quality, non-clinical, and clinical comments, including the following recommendations to the Applicant regarding clinical development:

- Provide a scientific rationale with supportive data to establish a bridge between US-licensed Enbrel and EU-approved Enbrel. A 3-way PK similarity study was recommended.
- Assess safety and immunogenicity in the setting of patients who undergo a single transition from comparator Enbrel to GP2015 to provide a descriptive comparison with patients who continue on comparator Enbrel.

There were no pre-BLA interactions to discuss the details of the format and content of the BLA.

6 CMC

Executive summary

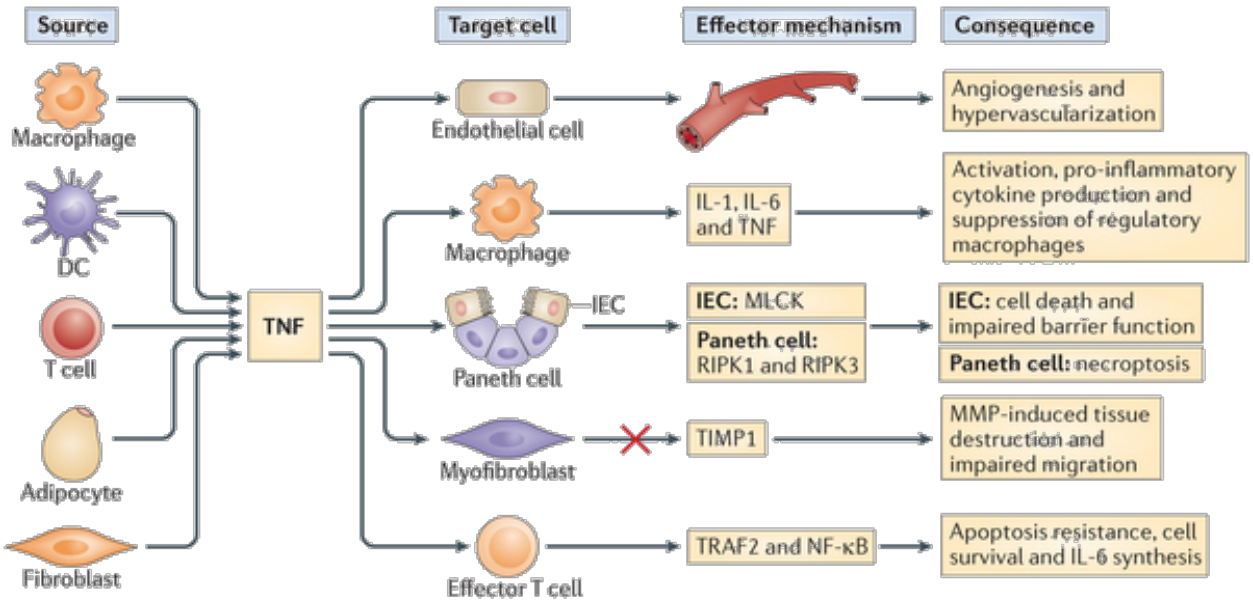
GP2015 is a proposed biosimilar to US-licensed Enbrel. An analytical similarity program was designed utilizing the proposed biosimilar, GP2015, US-licensed Enbrel and EU-approved Enbrel. The program had two goals: first, an analytical comparison of the proposed biosimilar to US-licensed Enbrel was needed to demonstrate findings that it is “highly similar” to the US-licensed Enbrel notwithstanding minor differences in clinically inactive components; and second, a comparison of US-licensed Enbrel to EU-approved Enbrel was needed to establish the analytical component of the scientific bridge to justify the relevance of data generated using EU-approved Enbrel as the comparator in some clinical and non-clinical studies. The results of these comparisons show that the three products met the pre-specified criteria for analytical similarity, including statistical criteria for the critical potency bioassay, TNF-α neutralization, and TNF-α binding. Thus, a pair-wise analytical comparison of GP2015 to US-licensed Enbrel supports the conclusion that GP2015 is highly similar to US-licensed Enbrel. Further, an adequate analytical bridge between EU-approved Enbrel, US-licensed Enbrel, and GP2015 was established as part of the scientific bridge to justify the relevance of the comparative data generated using EU-approved Enbrel to support a demonstration of the biosimilarity of GP2015 to US-licensed Enbrel.

Pathophysiologic Role of TNF-alpha and Mechanisms of Action of Etanercept

Tumor Necrosis Factor (TNF-α) is considered to be a master cytokine critical for the function of the immune system as well as inflammatory responses (Figure 1). It exists in two forms, both soluble and membrane-bound, that can be produced by a range of immune-related or other cell types. The consequences of TNF-α effector functions are varied and include tissue destruction, activation of pro-inflammatory cytokines and cell death. Thus, dysregulation of this master pro-inflammatory cytokine can have multiple clinical consequences in inflammatory conditions, such as rheumatic or dermatological diseases.

The 26 kDa membrane bound (mTNF-α) form and the 17 kDa soluble form (sTNF-α) both exist as non-covalently linked homotrimers. Because both forms are active, signals may be passed locally from cell-to-cell via mTNF:TNF-R interactions, or more distally through release of sTNF. Soluble TNF-α is generated following cleavage of mTNF-α by members of a class of metalloproteinases called “sheddases”, which include TNF-converting enzyme (TACE, ADAM17) and ADAM 10. Under normal physiological conditions, the concentration of TNF-α found in bodily fluids is almost undetectable, while stimulation by external sources can increase concentrations to measurable and sometimes very high levels. Biological responses to TNF-α are mediated through two structurally distinct, cognate TNF receptors, TNF-R1 (p55) and TNF-R2 (p75). These high affinity receptors are present as preassembled trimers on the cell surface. Most cells constitutively express TNF-R1 on their surface; in contrast, TNF-R2 is inducible and expressed preferentially on hematopoietic and endothelial cells.

Figure 1. TNF-α: A "Master Cytokine"



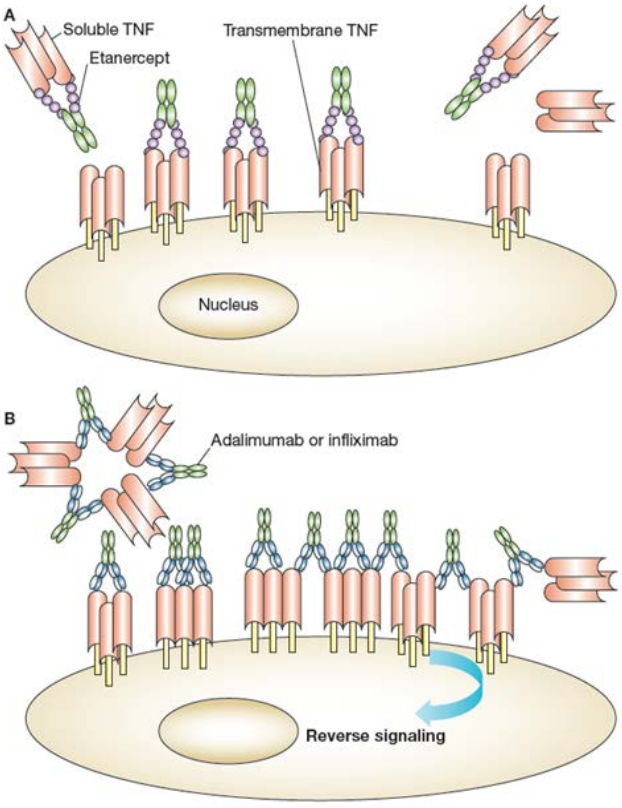
Source: Neurath, 2014[4]

Etanercept is a TNFR2-Fc fusion protein, with a high avidity for both soluble and membrane-bound TNF-α and Lymphotoxin (TNF-β), although TNF-α is considered to be the more relevant target for the clinical effect[5]. Etanercept functions via the TNFR2 portion by binding, neutralizing and sequestering excess sTNF-α produced in local inflammatory disease tissue sites. This major mechanism of action of etanercept is also the major mechanism of the anti-TNF monoclonal antibodies (mAbs); however, the ability of etanercept to function via additional mechanisms of action is either reduced relative to the anti-TNF mAbs or etanercept does not have the additional functions ascribed to some of the anti-TNF mAbs. For example, most studies show that etanercept is only capable of weakly inducing apoptosis relative to the anti-TNF mAbs or could not induce apoptosis of T cells or monocytes[6]. In studies where some apoptosis was observed, it is not clear if this is due to etanercept sequestration of sTNF to keep it from binding to the cells or reverse signaling subsequent to binding mTNF. Etanercept can also induce Fc mediated effector functions in vitro, such as antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) of mTNF-expressing inflammatory T-cells or other cells associated with particular disease states; however, the levels of these activities are low relative to intact anti-TNF-α monoclonal antibodies[7] and have not been demonstrated to play a role in the

[4] Neurath, M. Nature Reviews Immunology, 2014, 14(5), 329-342.
[5] Medvedev, AE. et al., J Bio Chem, 1996, 271(176),9778-9784; Kennedy, WP. et al., Arth Res & Therapy, 2014, 16:467-475.
[6] Oleson, CM. et al., Pharmacology & Therapeutics, 2016,159:110-119, and references therein.
[7] Arora, T. et al., Cytokine, 2009, 45: 124-131.

mechanism of action in the etanercept approved indications. Possible reasons for the differences between etanercept and the intact anti-TNF mAbs regarding Fc effector functions and the induction of apoptosis may be in how each binds TNF; each TNF antagonist has distinct binding sites on the TNF homotrimer[8] and etanercept is monovalent for both sTNF and mTNF, whereas the mAbs are bivalent and can form larger complexes[9] (Figure 2).

Figure 2. Etanercept and Anti-TNF mAbs Binding to mTNF



Source: Rigby 2007

GP2015 Manufacturing

GP2015 is produced using a mammalian cell line in large scale bioreactor culture followed by a drug substance purification process that includes various steps designed

[8] Kim, MS. et al., J Molecular Biology 2007, 374: 1374-1388; Liang, S. et al., 2013, J Biol Chem. 288(19) 13799 – 13807; Hu, S. et al., J Biol Chem. 288(38) 27059 – 27067.
[9] Rigby, WFC. Nature Clinical Practice Rheumatology 2007, 3(4) 227-233; ibid Arora et al. 2009.

to isolate and purify the protein product. Residual levels of process-related impurities, such as host cell proteins (HCP), host cell DNA (hcDNA) and other process-related impurities specific to the GP2015 process, were evaluated in GP2015 drug substance. Data were provided that demonstrate that the manufacturing process of GP2015 drug substance is able to reduce these impurities to very low levels (e.g., ppm for HCP and pg/mg for hcDNA), consistent with industry standards for biotechnology products.

GP2015 drug product was developed as a solution for injection in a pre-filled syringe or autoinjector with strengths, dosage forms, and routes of administration (25 mg/0.5 mL or 50 mg/1.0 mL) previously approved for US-licensed Enbrel for use in the treatment of the same indications as those approved for US-licensed Enbrel. The GP2015 formulation differs from that of US-licensed Enbrel. The GP2015 formulation includes a citrate buffer, whereas the US-licensed Enbrel formulation includes a phosphate buffer[10]. Note that US-licensed Enbrel is also available in a multiple-use vial as a lyophilized powder for reconstitution with Sterile Bacteriostatic Water for Injection. At this time, there is no GP2015 drug product developed as a lyophilized drug product.

Although there were no changes in the scale of the manufacturing process for GP2015 drug substance, the process was optimized during the clinical development program to improve purity and yield. To rule out the possibility of evolution or drift in product quality over time, Sandoz provided data demonstrating comparable product quality of GP2015 drug substances that were manufactured over the course of process development. The drug product manufactured for commercial launch was also shown to be comparable to the drug product manufactured by the clinical process.

The GP2015 final drug substance and drug product processes are validated, and the resultant product is of a consistent quality. The controls put in place for the manufacture of GP2015 drug substance and GP2015 drug product meet regulatory requirements. An assessment of the manufacturing facilities took place on March 3-7, 2016, by a team of Agency inspectors. The team verified that the drug substance and drug product sites are acceptable from a good manufacturing practice (GMP) perspective.

Analytical Similarity Assessment

Determining whether GP2015 is highly similar to US-licensed Enbrel, and establishing the adequacy of the analytical portion of the scientific bridge between GP2015, US-licensed Enbrel, and EU-approved Enbrel was accomplished by Sandoz's evaluation and comparison of analytical data from multiple lots of each of the three products. The FDA performed confirmatory statistical analysis of the submitted data, which is presented in further detail later in this section. Overall, 19 lots of GP2015 drug product (DP), 34 lots of US-licensed Enbrel DP and 50 lots of the EU-approved Enbrel DP were

[10] US-licensed Enbrel labeling approved on March 25, 2015, at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103795s5548lbl.pdf, retrieved May 26, 2016.

analyzed, although not all lots were assessed using each test. In addition, 18 lots of GP2015 drug substance (DS) were also analyzed, but results for GP2015 DS and GP2015 DP were not combined for the assessment of analytical similarity. Importantly, 8-9 lots of GP2015 DP, 11-13 lots of US-licensed Enbrel and 11-12 lots of the EU-approved Enbrel were used for analysis with critical assays that directly measure the primary mechanism of action of the product, TNF-α binding and neutralization. The number of lots analyzed using each assay was chosen by Sandoz, based on their assessment of the variability of the analytical method and availability of material.

The expiration dates of the US-licensed Enbrel lots and EU-approved Enbrel lots that were analyzed spanned approximately 8 years (2008 – 2016). The GP2015 DP lots that were used for analysis were manufactured between 2011 and 2014.

The analytical comparison of GP2015 with US-licensed Enbrel was used to support the Applicant's demonstration that GP2015 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components. Pairwise comparisons of GP2015, US-licensed Enbrel, and EU-approved Enbrel were used to support the analytical portion of the scientific bridge between the three products to justify the relevance of the comparative data generated using EU-approved Enbrel from some clinical and nonclinical studies.

The analytical similarity exercise used a comprehensive range of methods (see Table 1), which included orthogonal methods measuring the same critical quality attribute (CQA) from different perspectives. Many assays were designed to specifically address and measure potential mechanisms of action of etanercept, including TNF-α binding and neutralization, TNF-β neutralization, and Fc-mediated functions. TNF-α neutralization was studied by two methods: an NF-κB reporter gene assay where GP2015, US-licensed Enbrel or EU-approved Enbrel neutralize the ability of TNF to induce NF-κB expression; and the ability of GP2015, US-licensed Enbrel or EU-approved Enbrel to inhibit TNF-α mediated apoptosis. All methods were validated or qualified prior to the time of testing and were demonstrated to be suitable for their intended use.

Table 1. Quality Attributes and Methods Used to Evaluate Analytical Similarity of GP2015, US-licensed Enbrel, and EU-approved Enbrel

Quality Attribute	Methods
Primary structure	• Reduced Peptide mapping with ultraviolet (UV) and mass spectrometry (MS) detection • Mass analysis of peptides (ESI-MS) • Amino Acid Analysis • Post-translational modification (MS/MS) • Intact Mass (MALDI-TOF-MS) • Peptide mapping coupled with tandem mass spectrometry (MS/MS) • Disulfide bridging (non-reducing peptide mapping) • Free cysteines
Protein content	• UV/Vis spectroscopy
Higher order structure	• Far and Near UV circular dichroism • Differential scanning calorimetry • Hydrogen/Deuterium Exchange • FTIR • 1D-NMR • X-ray crystallography
High molecular weight species/aggregates	• Size exclusion chromatography (SEC-HPLC) • Size exclusion chromatography (SEC-MALLS) • Analytical Ultracentrifugation • FFF-MALLS • 2D-DIGE (charge and size)
Fragments	• CE-SDS • SEC
Charge and Hydrophobic variants	• CZE • Reversed phase chromatography (RPC-HPLC)
Glycosylation and glycosylation site occupancy	• Peptide mapping linked to ESI-MS (N-glycans) • NP-HPLC-MD (N-glycans – overall, TNFR portion and Fc portion) • MALDI-TOF (O-linked glycan analysis) • AEX, WAX and RP-HPLC of labeled N or N and O glycans (Sialic Acid analysis) • Boronate affinity chromatography (glycation)
In vitro Potency assays	• TNF-α neutralization assay reporter gene assay • TNF-β neutralization assay reporter gene assay • Cell based apoptosis inhibition assay
Binding assay – TNF-α	• Surface plasmon resonance
Binding assay – Fc and complement	• FcγRIIIa V and F type binding affinity (SPR) • FcγRI binding (SPR) • FcγRIIa binding (SPR) • FcγRIIIa binding affinity (SPR) • FcRn binding affinity (SPR) • C1q binding assay (ELISA)
Bioassay/mechanism of action exploration	• ADCC (NK cell line as effectors and engineered target cell expressing high levels of mTNF) • CDC (target cell stably transfected with a constitutively membrane-associated form of TNF- α

Primary Structure

To support a demonstration that the proposed biosimilar product is highly similar to US-licensed Enbrel, it is expected that the expression construct for a proposed biosimilar product will encode the same primary amino acid sequence as US-licensed Enbrel. To achieve this goal, expression constructs were designed to encode a protein sequence that matches US-licensed Enbrel by the GP2015 production cells. This can be confirmed at the protein level by methods such as N-terminal sequencing, intact mass spectroscopy, tandem mass spectroscopy and tryptic peptide mapping.

Peptide mapping

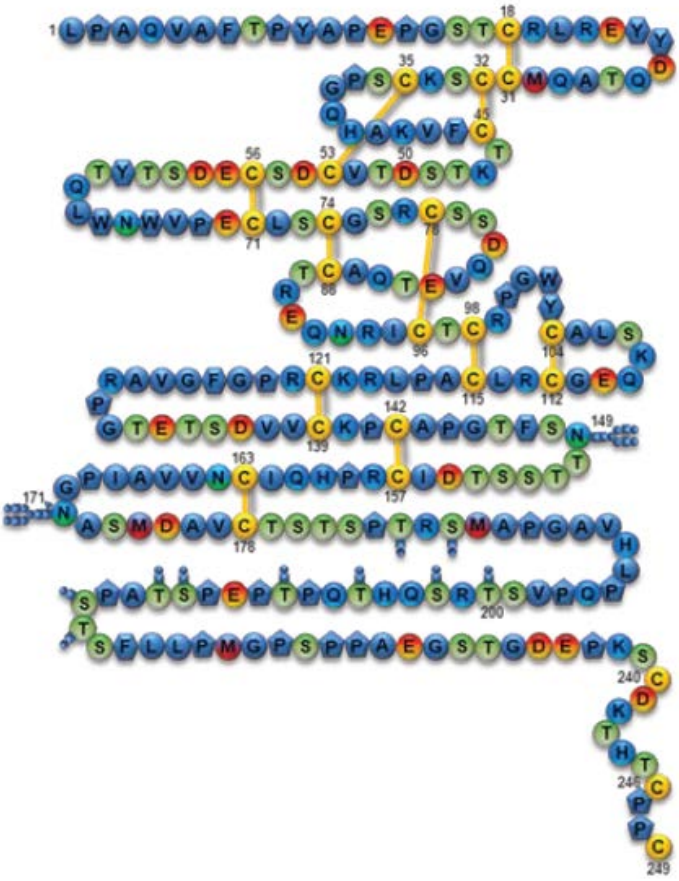
The primary structure of GP2015, US-licensed Enbrel and EU-approved Enbrel, as assessed by peptide map data obtained using four different sets of enzymes, demonstrated that the chromatographic profile (peptide map) and primary amino acid sequence matches that of US-licensed Enbrel and EU-approved Enbrel. No additional peptides or missing peptides were detected in the comparison among the three products. In addition, the Applicant established that the intact mass of desialylated etanercept, etanercept without N-glycans and etanercept without O-glycans were similar for GP2015, US-licensed Enbrel and EU-approved Enbrel and using MALDI-TOF.

Further primary structure analysis

The N-terminal sequence was determined using reducing peptide mapping in combination with mass spectrometry. The analysis confirmed that the first thirty-four amino acids of GP2015 (LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSK) are identical to the first thirty-four amino acids of US-licensed Enbrel and EU-approved Enbrel and are derived from TNFR2. In addition, the N-terminal heterogeneity was highly similar among the products. The C-terminal sequence and C-terminal heterogeneities were also highly similar among the products and confirmed to be the C-terminal sequence of an IgG1 antibody.

The disulfide bonding pattern of etanercept is complex. Each TNFR2 arm of etanercept contains eleven intrachain disulfide bonds and each Fc portion contains 2 intrachain disulfide bonds for a total of 26 intrachain disulfide bonds. In addition there are three interchain disulfide bonds in the IgG1 Fc hinge region. Analysis by non-reducing peptide mapping using RP-HPLC separation followed by mass spectrometry confirmed the expected presence of all interchain and intrachain disulfide bonds in each of the three products. Figure 3 shows a structural representation of the intrachain disulfide bonds in the TNFR2 portion of GP2015.

Figure 3. Representation of TNFR Intrachain Disulfide Bonds



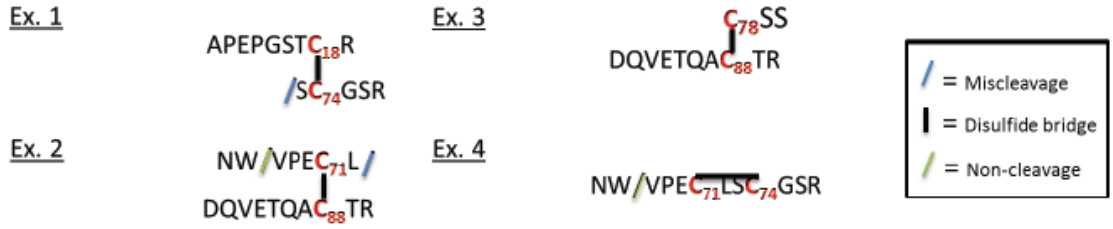
Source: Figure from the Sandoz 351(k) BLA submission

However, etanercept is known to also contain incorrect disulfide bond variants that can affect the potency of the product[11]. Figure 4 shows a representation of the incorrect disulfide bonds found in GP2015.

Using non-reducing peptide mapping, Sandoz quantified the levels of peptide T7, which contains the incorrect disulfide bond Ex.3 in GP2015, US-licensed Enbrel and EU-approved Enbrel. GP2015 contains lower levels of this incorrect disulfide bond relative to US-licensed Enbrel and EU-approved Enbrel (Table 2).

[11] US Patent 7,294,481, 2007, at http://www.google.com/patents/US7294481, retrieved May 26, 2016: Goswami. S. et al., Antibodies, 2013, 2:452-500.

Figure 4. Incorrect Interchain Disulfide Bonds in GP2015



Source: Figure from the Sandoz 351(k) BLA submission

Table 2. Descriptive Statistics for the T7 Peptide Data of GPP2015, US-licensed Enbrel, and EU-approved Enbrel

Product	Number of batches	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
GP2015	9	1.21	0.11	1.1	1.4
US-licensed Enbrel	13	2.15	0.36	1.7	2.7
EU-approved Enbrel	11	2.21	0.31	1.7	2.8

Source: FDA analysis of data from Sandoz 351(k) BLA submission

In addition, the Applicant provided data demonstrating a correlation between levels of the T7 peptide and potency, where lots with higher levels of the T7 peptide had lower potency in the TNF-α neutralization assay. The relationship between incorrect disulfide bonds and potency is discussed in detail in the section describing biological activity.

Protein Content

US-licensed Enbrel is filled in pre-filled syringes at 50 mg etanercept per mL in two strengths: 25 mg/0.5mL and 50 mg/1.0 mL. The drug product manufacturing process of GP2015 was designed to match the protein content of US-licensed Enbrel, within reasonable manufacturing tolerances. Both presentations of GP2015, US-licensed Enbrel and EU-approved Enbrel were used to compare the protein content by UV/VIS spectroscopy. The data confirm that total protein amounts in the 25 mg/0.5 mL and 50 mg/1.0 mL pre-filled syringes of GP2015, US-licensed Enbrel and EU-approved Enbrel met pre-specified acceptance criteria.

Aggregates

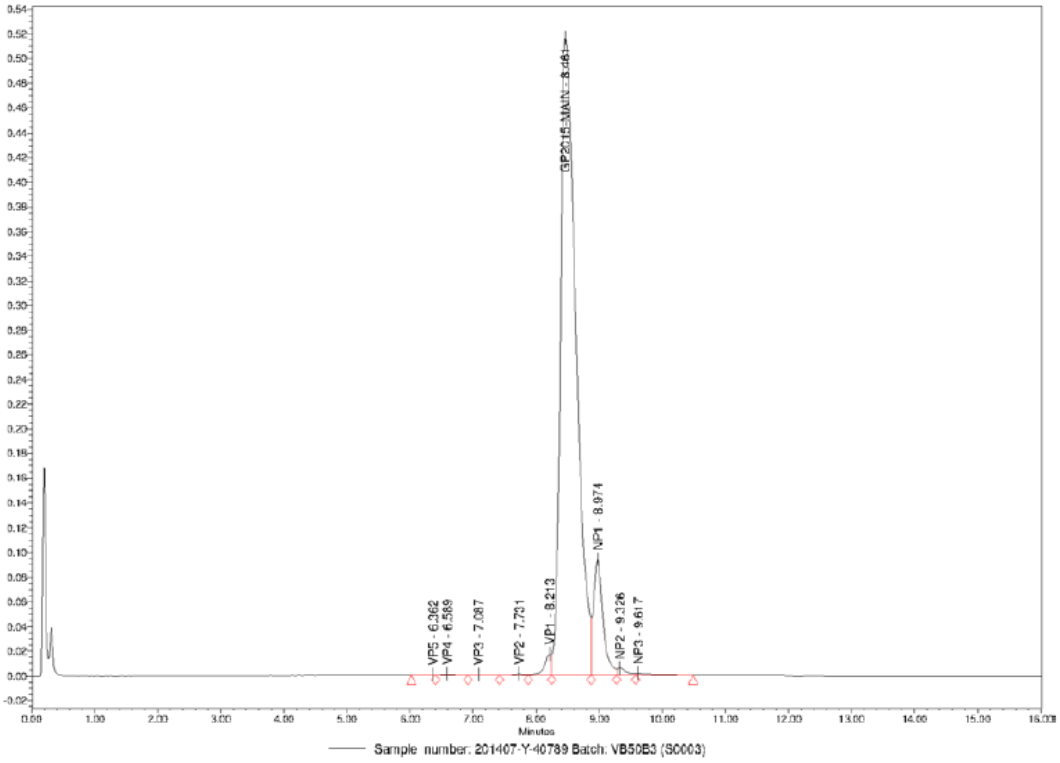
Biopharmaceuticals typically contain very low levels of protein aggregates (<1%) at release, which increase with the age of the product. They are measured and controlled at lot release and by long term stability studies. Small amounts of aggregation are present in both GP2015 and US-licensed Enbrel. Aggregation is typically detected and quantified by the size-exclusion chromatography assay (SEC-HPLC). The average

level of aggregates in US-licensed Enbrel quantified by Sandoz's SEC-HPLC assay was 2.1%, while GP2015 was 0.4%. Overall, GP2015 has lower levels of aggregates compared with US-licensed Enbrel. This may be in part due to differences in the ages of the lots at the time they were tested, but some aged GP2015 lots also had lower levels of aggregates compared with US-licensed Enbrel. From a quality standpoint, high levels of aggregation may impact product immunogenicity when infused into patients, but levels up to 3% at the end of shelf life are typical for biotechnology products.

Hydrophobic Variants

Some product variants differ in hydrophobicity and can be separated by reversed-phase HPLC (RP-HPLC). Figure 5 shows the RPC profile of GP2015. The peak following the main peak, termed "post-peak" contains a variety of product-related species, but the major species in this peak contains misfolded protein due to incorrect disulfide bond formation. GP2015 has lower levels of the "post-peak" compared with US-licensed Enbrel and EU-approved Enbrel, consistent with lower levels of the T7 peptide. Table 3 provides the descriptive statistics. The differences in levels of the RPC "post-peak" in GP2015 compared with US-licensed Enbrel and EU-approved Enbrel could affect the outcomes of measures of potency.

Figure 5. RPC-Chromatogram of GP2015



Source: Figure from the Sandoz 351(k) BLA submission

Table 3. Descriptive Statistics for the RPC "Post-Peak" Data of GPP2015, US-licensed Enbrel, and EU-approved Enbrel

Product	# of lots	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
GP2015	19	10.73	0.62	9.6	11.8
US-licensed Enbrel	21	16.16	1.91	10.2	17.4
EU-approved Enbrel	26	17.54	2.01	12.3	19.8

Source: FDA analysis of data from Sandoz 351(k) BLA submission

Biological Activity

A number of bioassays were designed and qualified to evaluate potential etanercept functions, including binding and neutralization of TNF-α, neutralization of TNF-β (lymphotoxin), as well as Fc effector functions. The data are generally reported as a percentage relative to the Applicant's in-house GP2015 reference standard.

TNF-α binding

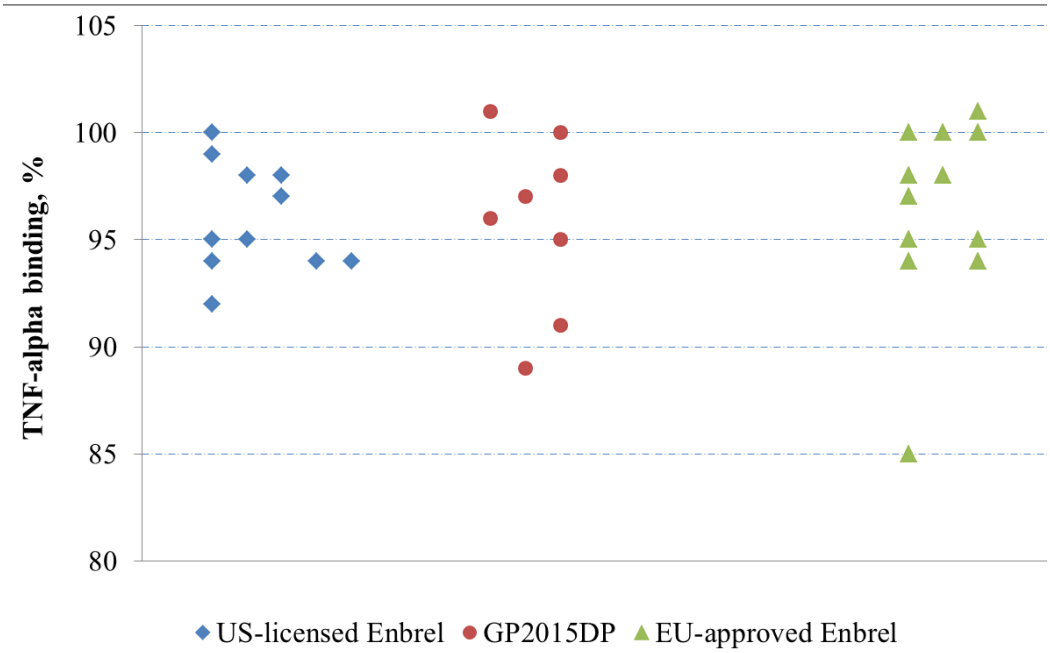
TNF-α binding was assessed using a competitive surface plasmon resonance (SPR) method. Different concentrations of etanercept are incubated with a fixed concentration of TNF-α to achieve a steady-state equilibrium between bound and free TNF-α . The mixture is then passed over a sensorchip coupled with an anti-TNF monoclonal antibody, to which only free TNF-α will bind. A comparison of the relative TNF-α binding of GP2015, US-licensed Enbrel, and EU-approved Enbrel for TNF-α was carried out with 8 to 12 lots of each product (Figure 6 and Table 4). Because of the criticality of this function, these data were subjected to a statistical analysis using equivalence testing. The TNF-α potency of GP2015 is statistically equivalent to the TNF-α binding affinity of US-licensed Enbrel if the 90% confidence interval (CI) of the mean difference in TNF-α binding (by competitive SPR) between GP2015 and US-licensed Enbrel is entirely within an equivalence acceptance criterion calculated from Sandoz's data on US-licensed Enbrel. Equivalence testing results for the TNF-α binding data of GP2015, US-licensed Enbrel, and EU-approved Enbrel are shown in Table 5.

Table 4. Descriptive Statistics for the TNF-α Binding Data

Product	# of lots	Sample mean %	Sample standard deviation	Min, %	Max, %
US-licensed Enbrel	11	96.00	2.53	92	100
GP2015	8	95.88	4.16	89	101
EU-approved Enbrel	12	96.42	4.38	85	101

Source: FDA analysis of data from Sandoz 351(k) BLA submission

Figure 6. Comparative Potency (Competitive SPR) of GP2015, US-licensed Enbrel, and EU-approved Enbrel to Human TNF-α



Source: FDA analysis of data from Sandoz 351(k) BLA submission

Table 5. Equivalence Testing Results for the TNF-α Binding

Comparison	# of lots	Mean difference	90% confidence interval for mean difference	Equivalence margin	Equivalent
GP2015 vs. US	(8, 11)	-0.125	(-3.11, 2.86)	(-3.80, 3.80)	Yes
GP2015 vs. EU	(8, 12)	-0.542	(-3.94, 2.94)	(-6.57, 6.57)	Yes
EU vs. US	(12, 11)	0.417	(-2.14,2.98)	(-3.80, 3.80)	Yes

Source: FDA analysis of data from Sandoz 351(k) BLA submission

The statistical equivalence analyses shown in Table 5 support the conclusion that GP2015 is highly similar to that of US-licensed Enbrel. Further, these analyses support the analytical component of the scientific bridge between US-licensed Enbrel, EU-approved Enbrel and GP2015 to justify the relevance of comparative data generated from clinical and nonclinical studies that used EU-approved Enbrel.

TNF-α neutralization assay – Reporter Gene Assay

The primary mechanism of action of the three products was also measured using an *in vitro* TNF-α neutralization assay. This assay measures the ability of etanercept to neutralize TNF-α in a reporter gene assay (TNF-α RGA) using HEK293 cells stably transfected with a luciferase reporter gene construct under the control of an NF-κB-dependent promoter. When cultured with TNF-α, luciferase expression is induced, but

expression is inhibited when increasing amounts of etanercept are added to the culture. A comparison of the relative TNF-α neutralization of GP2015, US-licensed Enbrel and EU-approved Enbrel was carried out with 19 to 43 lots of each product. Descriptive statistics for the *in vitro* TNF-α neutralization RGA data show that the results of all 19 GP2015 lots were within the minimum/maximum range of the data from the 31 US-licensed Enbrel lots, but the means are different by >10% and GP2015 has a higher mean potency (Table 6).

Table 6. Descriptive Statistics for the *in vitro* TNF-α Neutralization RGA Data of GP2015, US-licensed Enbrel, and EU-approved Enbrel

Product	# of lots	Sample mean %	Sample standard deviation	Min, %	Max,%
US-licensed Enbrel	31	86.94	6.85	80	103
GP2015	19	96.95	2.37	93	101
EU-approved Enbrel	43	91.36	9.00	76	118

Source: Data from Sandoz 351(k) BLA submission

These data were also subjected to a statistical analysis using equivalence testing with a 90% confidence interval (CI) (Figure 7 and Table 7). The *in vitro* TNF-α neutralization activity of GP2015 was not statistically equivalent to the *in vitro* TNF-α neutralization activity of US-licensed Enbrel using the criteria that the 90% confidence interval (CI) of the mean difference in the *in vitro* TNF-α neutralization activity between GP2015 and US-licensed Enbrel should be entirely within an equivalence acceptance criterion calculated from the Applicant's data on US-licensed Enbrel. However, among the two-way comparisons, the *in vitro* TNF-α neutralization activity of GP2015 was statistically equivalent to EU-approved Enbrel, and US-licensed Enbrel and EU-approved Enbrel also met the criteria for equivalence (Table 7).

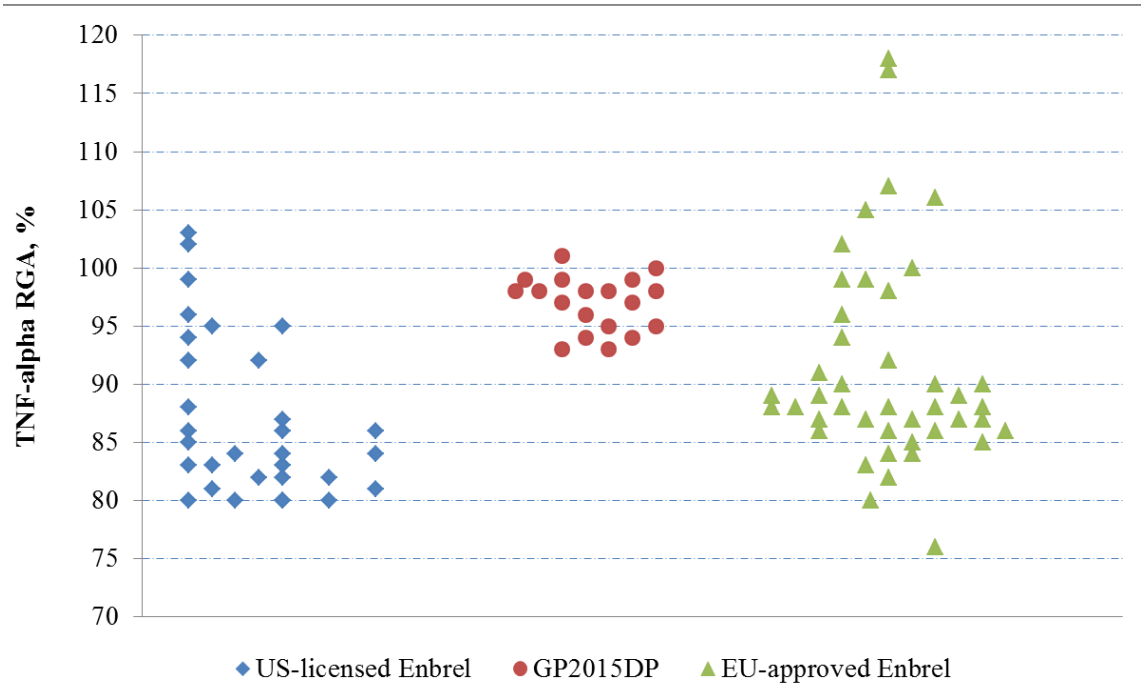
The statistical equivalence analysis shown in Figure 7 and Table 7 regarding the *in vitro* TNF- α neutralization activity of GP2015 does not support the conclusion that GP2015 is highly similar to that of US-licensed Enbrel.

Table 7. Equivalence Testing Results for the *in vitro* TNF-α Neutralization RGA of GP2015, US-licensed Enbrel, and EU-approved Enbrel

Comparison	# of lots	Mean difference	90% confidence interval for mean difference	Equivalence margin	Equivalent
GP2015 vs. US	(19,31)	10.01	(7.62, 12.36)	(-10.28, 10.28)	No
GP2015 vs. EU	(19,43)	5.62	(3.15, 8.59)	(-13.50, 13.50)	Yes
EU vs. US	(43,31)	4.39	(1.32, 7.46)	(-10.28, 10.28)	Yes

Source: FDA analysis of data from Sandoz 351(k) BLA submission

Figure 7. TNF-α RGA of GP2015, US-licensed Enbrel, and EU-approved Enbrel



Source: FDA analysis of data from Sandoz 351(k) BLA submission

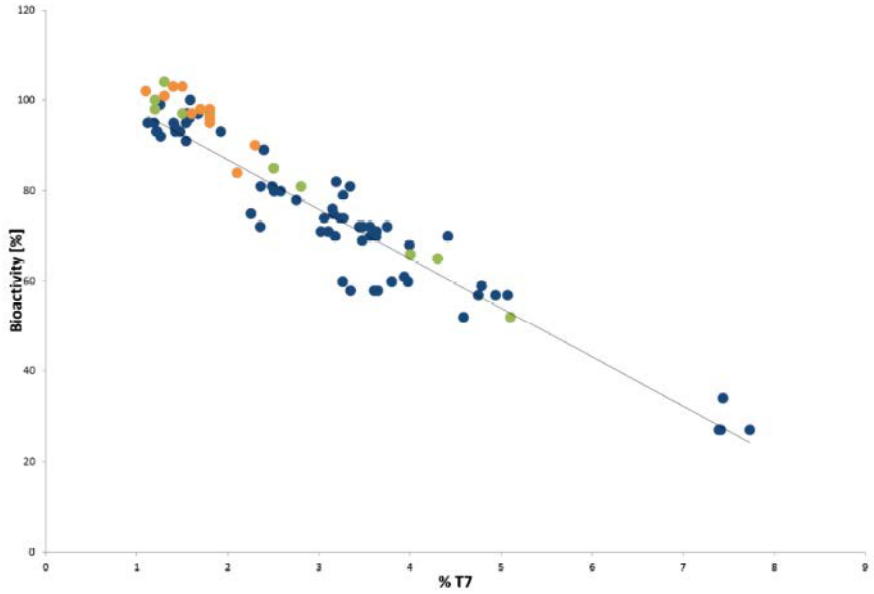
Given that the ability of etanercept to neutralize TNF-α is the primary mechanism of action and that there are differences in the levels of the T7 peptide and the RPC "post-peak", which are associated with lower potency, the Agency requested that the Applicant further explore the relationship between levels of the T7 peptide and potency, and whether the incorrect disulfide bonds could correctly reform in vivo or under in vitro conditions designed to mimic in vivo conditions in blood. This request was based on a growing body of literature demonstrating that serum proteins such as antibodies and cell surface proteins such as TNFR contain disulfide bonds that can rearrange *in vivo*[12].

No information could be obtained from PK studies, because the bioanalytical method to assess the PK of GP2015, US-licensed Enbrel and EU-approved Enbrel cannot distinguish the correctly folded protein from the misfolded protein. In addition, *in vitro* serum stability studies were inconclusive. However, the Applicant compared the levels of T7 peptide and bioactivity in the TNF-α RGA assay of GP2015 drug substance and GP2015 process intermediates with and without incubation *in vitro* in the presence of a

[12] Liu, YD. et al., J. Biol Chem, 2008, 283(43): 29266 – 29272; Liu, YD, et al., Molecular Immunology, 2013, 54:217 – 226; Ouellette, D., et al., Analytical Biochem., 2010, 397:37-47; Rispens, T., J. Am Chem Soc., 2011, 133: 10302 – 10311; van der Neut Kolfschoten, M, et al., Science, 2007, 317: 1554 – 1557; Wang, T., et al., J of Pharm an Biomed Analysis, 2015, 102: 519-528; Butera, D, et al., Blood, 2014, 123:2000 – 2007; Park, MS., et al, Scientific Reports, 2016, 6:1-12; Soderberg, A. et al., Antioxidants and Redox Signaling, 2013, 18:363-375.

redox buffer. The process intermediates were chosen because they have higher levels of the T7 peptide and RPC "post-peak". These preliminary experiments demonstrated that under redox conditions *in vitro*, there was a reduction of the levels of the T7 peptide and a restoration of potency. For example, one of the process intermediates contained 4.3% T7 peptide with 65% activity using the TNF-α RGA assay. After the redox incubation, the T7 peptide levels were reduced to 2.3% and bioactivity increased to 90%. Subsequent studies repeated the experiment with additional lots of GP2015, US-licensed Enbrel, and EU-approved Enbrel. Figure 8 shows that the results from the control (green dots) and redox samples (orange dots) fit with the previous knowledge of the structure-function relationship between the presence of the T7 peptide and bioactivity (blue dots).

Figure 8. Structure-Function Relationship Between the T7 Peptide and Bioactivity

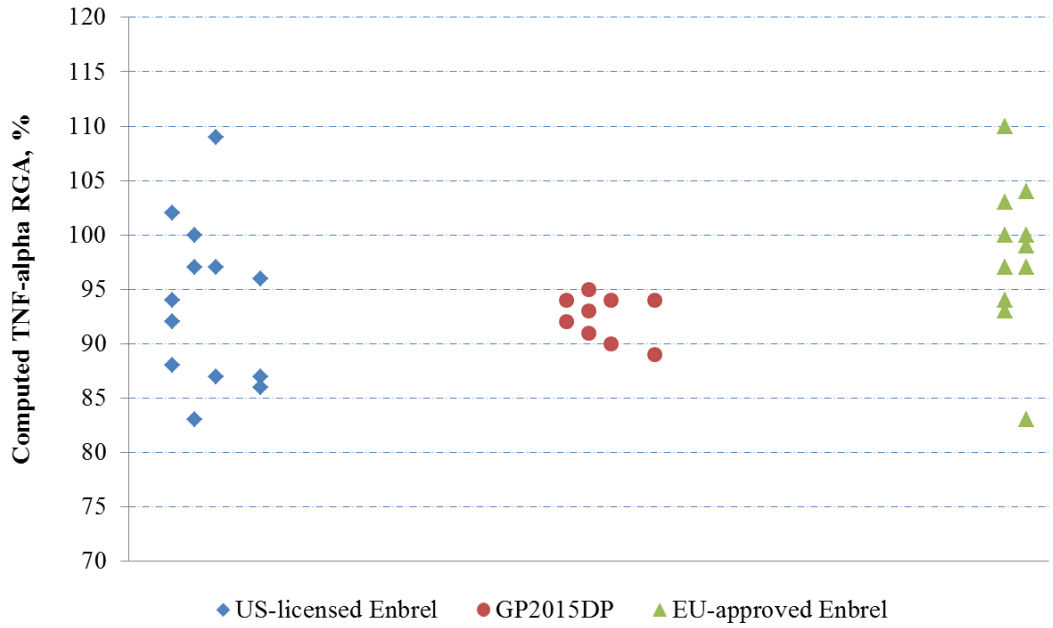


Source: Figure from the Sandoz 351(k) BLA submission

Using these data, Sandoz developed a computed potency model that could be used to determine the adjusted potency of GP2015, US-licensed Enbrel, and EU-approved Enbrel lots for which the level of the T7 peptide had been determined. At the request of the Agency, Sandoz also performed a sensitivity analysis assuming only 50% of the incorrect disulfide bonds reformed and Sandoz also included a robustness analysis of their model.

A comparison of the relative TNF-α neutralization of GP2015, US-licensed Enbrel, and EU-approved Enbrel using the computed potency model was carried out with 9 to 13 lots of each product and subjected to a statistical analysis using equivalence testing with a 90% confidence interval (CI) (Figure 9 and Table 8 and 9).

Figure 9. TNF-α RGA of GP2015, US-licensed Enbrel, and EU-approved Enbrel Based on the Computed Potency Model



Source: FDA analysis of data from Sandoz 351(k) BLA submission

Table 8. Descriptive Statistics for the *in vitro* TNF-α Neutralization RGA Data of GP2015, US-licensed Enbrel, and EU-approved Enbrel Based on the Computed Potency Model

Product	# of lots	Sample mean %	Sample standard deviation	Min, %	Max, %
US-licensed Enbrel	13	93.69	7.47	83	109
GP2015	9	92.44	2.07	89	95
EU-approved Enbrel	11	98.18	6.94	83	110

Source: Data from Sandoz 351(k) BLA submission

Table 9. Equivalence Testing Results for the *in vitro* TNF-α Neutralization RGA of GP2015, US-licensed Enbrel, and EU-approved Enbrel Based on the Computed Potency Model

Comparison	# of lots	Mean difference	90% confidence interval for mean difference	Equivalence margin	Equivalent
GP2015 vs. US	(9,131)	-1.25	(-5.08, 2.59)	(-11.20, 11.20)	Yes
GP2015 vs. EU	(9,11)	-5.74	(-9.66, -1.81)	(-10.41, 10.41)	Yes
EU vs. US	(11,13)	4.49	(-0.57, 9.55)	(-11.20, 11.20)	Yes

Source: FDA analysis of data from Sandoz 351(k) BLA submission

The statistical equivalence analyses shown in Table 9 support the conclusion that GP2015 is highly similar to that of US-licensed Enbrel. Further, these analyses support the analytical component of the scientific bridge between US-licensed Enbrel, EU-approved Enbrel and GP2015 to justify the relevance of comparative data generated from clinical and non-clinical studies that used EU-approved Enbrel.

TNF-α neutralization assay – Apoptosis

In addition to inducing de novo gene expression, signaling through TNFR can also induce apoptosis. Therefore, a cell based apoptosis method using the monocytic cell line U937, was used as an orthogonal method to assess the ability of GP2015, US-licensed Enbrel, and EU-approved Enbrel to neutralize TNF-α activity. 100% of the GP2015 lots were within the quality range set by US-licensed Enbrel (Figure 10 and Table 10).

Figure 10. TNF-α Neutralization by Apoptosis of GP2015, US-licensed Enbrel, and EU-approved Enbrel

Source: FDA analysis of data from Sandoz 351(k) BLA submission

Table 10. Descriptive Statistics for the *in vitro* TNF-α Neutralization Apoptosis Data of GP2015, US-licensed Enbrel, and EU-approved Enbrel

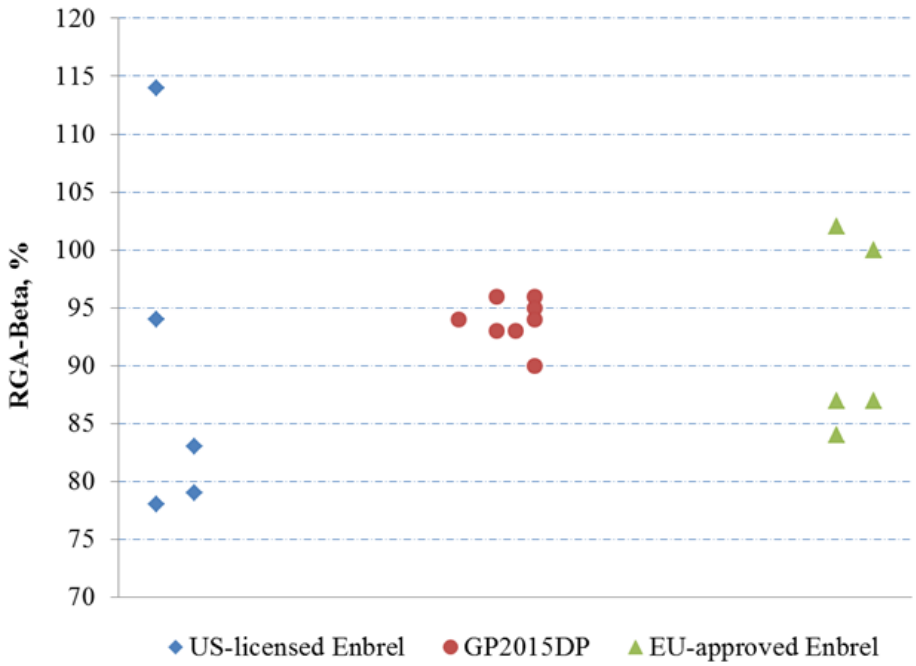
Product	# of lots	Sample mean %	Sample standard deviation	Min, %	Max, %
US-licensed Enbrel	11	117.7	10.25	99	134
GP2015	8	101.0	5.50	92	109
EU-approved Enbrel	11	112.1	13.5	92	133

Source: FDA analysis of data from Sandoz 351(k) BLA submission

TNF-β (Lymphotoxin) neutralization assay – Reporter Gene Assay

This assay measures the ability of etanercept to neutralize TNF-β in a reporter gene assay (TNF-β RGA) using the same system as for the TNF-α method, except the cells are incubated with TNF-β instead of TNF-α. 100% of the GP2015 lots were within the quality range set by US-licensed Enbrel (Figure 11, Table 10, and Table 11).

Figure 11. TNF-β Neutralization RGA of GP2015, US-licensed Enbrel, and EU-approved Enbrel



Source: FDA analysis of data from Sandoz 351(k) BLA submission

Table 11. Descriptive Statistics for the *in vitro* TNF-β Neutralization RGA Data of GP2015, US-licensed Enbrel, and EU-approved Enbrel

Product	# of lots	Sample mean %	Sample standard deviation	Min, %	Max, %
US-licensed Enbrel	5	89.6	15.04	78	114
GP2015	8	93.9	1.96	90	96
EU-approved Enbrel	11	112.1	13.5	92	133

Source: FDA analysis of data from Sandoz 351(k) BLA submission

Summary of TNF Binding and Neutralization Data

Two analytical methods representing the major mechanism of action of etanercept, TNF-α binding and TNF-α neutralization were assessed by statistical equivalence. The initial data from the TNF-α neutralization RGA assay for GP2015 and US-licensed Enbrel did not meet statistical equivalence. However, due to an understanding of the structure-function relationship between a product related impurity containing incorrect disulfide bonds and potency, the Applicant was able to establish a computed potency model based on in vitro redox conditions that were established to be consistent with *in vivo* conditions in blood[13]. Using this model, GP2015 and US-licensed Enbrel were shown to be statistically equivalent. The pairwise comparisons between GP2015 and EU-approved Enbrel, and US-licensed Enbrel and EU-approved Enbrel met statistical equivalence under both conditions.

The increased levels of incorrect disulfide bonds in both US-licensed Enbrel and EU-approved Enbrel did not affect TNF-α binding by competitive SPR, which met criteria for statistical equivalence. It is not clear why the TNF-α neutralization RGA assay would be more sensitive to differences in levels of incorrect disulfide bonds than TNF-α binding. In addition, the increased levels of incorrect disulfide bonds in both US-licensed Enbrel and EU-approved Enbrel did not appear to affect the activities of TNF-α neutralization by apoptosis and TNF-β neutralization RGA, as evaluated with a quality range. However, for the TNF-α neutralization by apoptosis and TNF-β neutralization RGA assays, there was greater variability in the results for US-licensed Enbrel and EU-approved Enbrel compared with GP2015. All GP2015 lots were within the quality ranges determined for these methods.

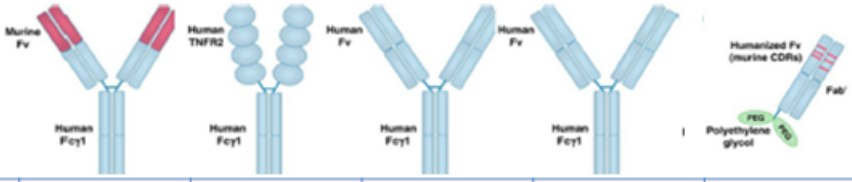
Fc function

The Fc region (constant region) of an antibody heavy chain contains amino acid residues that interact with complement C1q and Fc receptors to impart effector functions such as complement dependent cytotoxicity (CDC) and antibody dependent cellular cytotoxicity (ADCC). As discussed above, although etanercept can bind to these effector molecules and demonstrate both CDC and ADCC activity in vitro, this

[13] Ibid Liu et al 2013

activity is low relative to the activity of anti-TNF antibodies. This may be due in part to the monovalency of etanercept (Figure 2), which can be overcome by increasing the avidity for FcR and complement with the addition of tandem Fc regions[14]. Figure 12 summarizes the role of the Fc region in different TNF antagonist molecules.

Figure 12. The Role of Fc in the Anti-TNF-α Class Mechanism(s) of Action



	Infliximab	Etanercept	Adalimumab	Golimumab	Cerotlizumab (pegol)
ADCC	Moderate	Low	Moderate	Moderate	None
CDC	Moderate	Low	Moderate	Moderate	None
RA	Yes	Yes	Yes	Yes	Yes

Source: FDA summary of existing literature on the topic of Fc functions of TNF-blockers.[15]

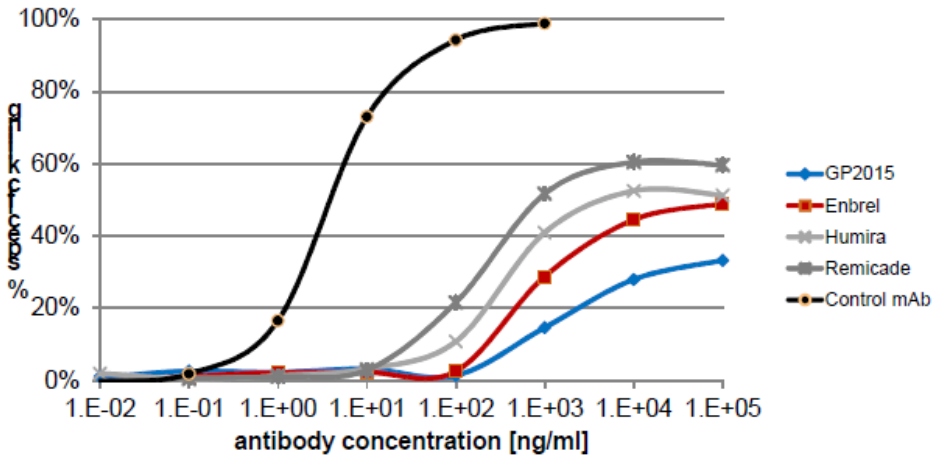
ADCC activity

ADCC was assessed using a natural killer (NK) cell line and fluorescently labeled HEK293 target cells that stably express a constitutive membrane-associated TNF-α. The addition of GP2015, US-licensed Enbrel or EU-approved Enbrel to the cell culture will induce ADCC activity, which is measured by release of the fluorescent dye. GP2015 has lower ADCC activity relative to US-licensed Enbrel and EU-approved Enbrel. This is consistent with lower levels of afucosylated Fc glycan structures on GP2015, because fucose has been shown to interfere with binding to FcγRIII, the Fc receptor expressed on NK cells. However, the Applicant provided data consistent with published literature demonstrating that the ADCC activity of etanercept is low in this assay relative to anti-TNF mAbs, and both etanercept and the anti-TNF mAbs have low ADCC activity relative to a control mAb with known ADCC activity (Figure 13).

Using LPS stimulated primary human monocytes as target cells and the NK cell line as effector cells, which represents more physiological conditions, neither GP2015, US-licensed Enbrel, nor EU-approved Enbrel were able to induce ADCC activity to a great extent, in contrast to the positive control antibody, alemtuzumab (Lemtrada) (Figure 14).

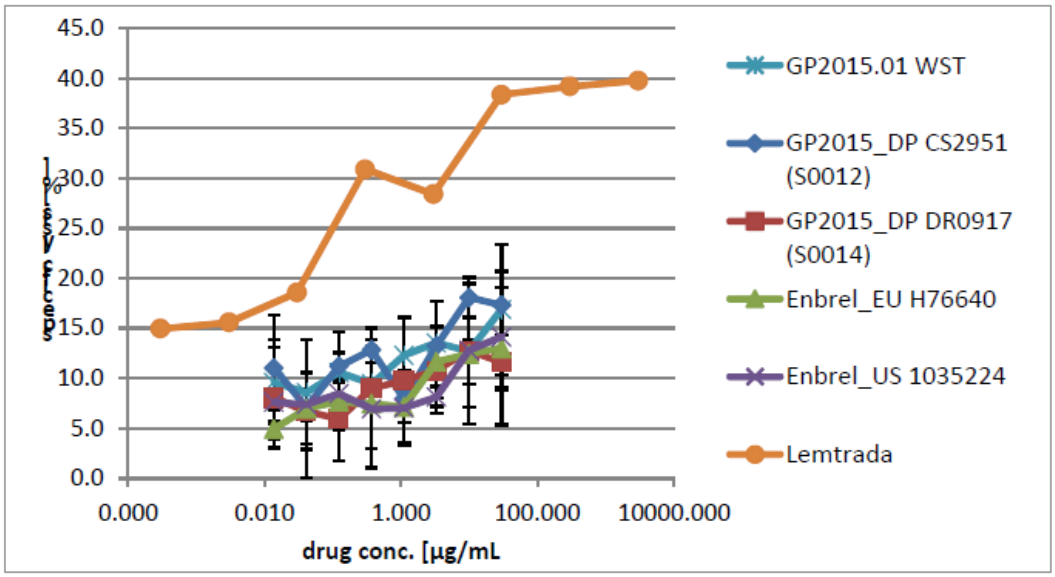
[14] Nagashima, H., et al., J Biochem, 2011, 149(3), 337-346
[15] Arora, T., et al. Cytokine, 2009 45(2), 124-131; Kaymakcalan, Z. et al. Clinical immunology, 2009, 131(2), 308-316; Mitoma, H. et al. Gastroenterology, 2005, 128(2), 376-392.

Figure 13. Comparison of Different TNF antagonists in the ADCC Assay



Source: Figure from the Sandoz 351(k) BLA submission

Figure 14. ADCC activity of GP2015, US-licensed Enbrel, and EU-Approved Enbrel of LPS Primary Human Monocytes by an NK Cell Line



Source: Figure from the Sandoz 351(k) BLA submission

CDC activity

CDC activity was assessed using Jurkat T cells stably transfected with a constitutive membrane-associated TNF-α incubated with human serum as a source of complement. Overall, GP2015 had higher CDC activity compared with US-licensed Enbrel and EU-approved Enbrel, but the Applicant provided data consistent with published literature demonstrating low CDC activity relative to anti-TNF mAbs. In addition, GP2015 drug

product had similar binding to human C1q as US-licensed Enbrel and EU-approved Enbrel.

Binding to Fc Receptors

The Fc- receptors, FcγRI, FcγRII, FcγRIII, FcRn, are diverse in structure and cell type expression. The predominant Fc receptor type on NK cells is FcγRIII (a or b forms), while other leukocytes express a broader range of Fc receptors. However, FcγRI and FcγRII isoforms may contribute to effector function, depending on the effector cell type at the site of disease. The neonatal Fc receptor, FcRn, plays in important role in IgG homeostasis, by binding the Fc region in a pH dependent manner and protecting the molecule from lysosomal degradation, thus prolonging the half-life of the molecule. Therefore binding to both Fcγ receptors and FcRn was assessed using SPR. The affinities of GP2015, US-licensed Enbrel and EU-approved Enbrel were similar for binding to FcγRI, FcγRIIa, FcγRIIb, FcγRIII F158, FcγRIII V158, and FcRn (data not shown).

Summary of Fc Function

Fc function was assessed by ADCC and CDC bioassays, as well as by binding to C1q, Fcγ receptors and FcRn using SPR. Although there were some differences between GP2015 and US-licensed Enbrel and EU-approved Enbrel in the ADCC and CDC bioassays, data provided were consistent with published literature showing that these activities for etanercept are low relative to anti-TNF mAbs. In addition, the binding affinities of GP2015 and US-licensed Enbrel and EU-approved Enbrel for C1q, Fcγ Receptors and FcRn were highly similar.

Higher Order Structure (HOS)

Secondary and tertiary structures of the etanercept products were evaluated by far and near UV circular dichroism (CD), Fourier Transform Infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), Hydrogen/Deuterium Exchange (HDX), 1D-NMR, and X-ray crystallography (Table 1). Proper folding is critical for the effective function and serum half-life of proteins.

Far and near UV CD spectroscopy provides information regarding secondary (α-helix, β-sheet and random coil structures) and tertiary structure, respectively. FTIR also provides information on secondary structure. All three methods resulted in overlapping spectra among 8 lots of GP2015 and 3 lots each of US-licensed Enbrel and EU-approved Enbrel.

DSC measures the unfolding of a protein when heated. Different subunits of a protein unfold at different melting temperatures (Tms). The thermograms were overlapping among 8 lots of GP2015 and 3 lots each of US-licensed Enbrel and EU-approved Enbrel and both Tm1 and Tm2 were consistent among all lots.

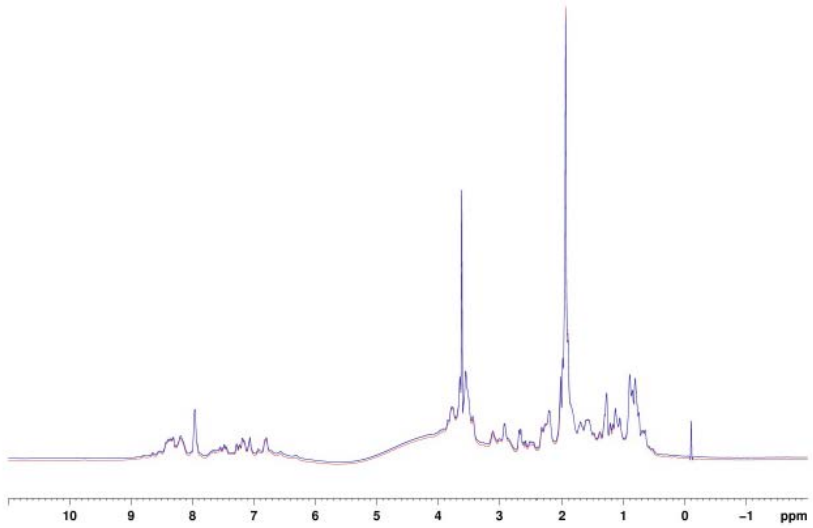
HDX followed by MS provides information on protein structure and dynamics. When incubated in heavy water (D_2O), the protein backbone amide hydrogens can exchange with deuterium and the rate of exchange is dependent on the local environment. For example, hydrogens in a disordered region exchange faster than those in a more structured region of the protein. After the exchange reaction is stopped by acidic pH and lowering the temperature, the protein is digested and the resulting peptides are separated and analyzed by RP-HPLC-ESI-MS. When deuterium replaces hydrogen in the peptide backbone, the mass of the peptide increases by 1 Da. The results are displayed as a heat map showing the exchange rate at each position after various incubation times. Faster exchange rates are represented by more intense colors. In Figure 15, GP2015 is represented in the top rows and US-licensed Enbrel is in the bottom row. Within each row, an increase in the color intensity can be seen, indicating different incubation times from 0 to 240 minutes. The Applicant provided additional analyses of the heat map comparing the fractional uptake of deuterium between the two lots and a difference plot of the results. The differences between the products were not more than 1 Da across the entire sequence.

Figure 15. HDX Heat Map for GP2015, US-licensed Enbrel, and EU-approved Enbrel

Source: Figure taken from the Sandoz 351(k) BLA submission

Nuclear magnetic resonance spectroscopy (NMR) can be used to determine the structure of small molecules and small proteins, but for larger proteins such as antibodies and receptor-fusion proteins, it can be provide a fingerprint that can demonstrate similarity between molecules. GP2015 and US-licensed Enbrel have highly similar 1D 1H NMR spectra (Figure 16).

Figure 16. 1D 1H NMR spectrum (overlay) of GP2015 US-licensed Enbrel



GP2015 (blue); US-licensed Enbrel (red) Source: Figure taken from the Sandoz 351(k) BLA submission

Glycan Structures

Etanercept is a glycoprotein containing up to 28 O-glycans and 2 N-glycans on the TNFR portion of the molecule and one N-glycan on the Fc region. LC-ESI-MS was used to determine the site occupancy of the O-glycans and all three products were shown to be similar regarding the core structures and variants detected at each site.

The N-glycan structures were determined for the intact molecules, as well as for the Fc and TNFR portions of etanercept after digestion with the enzyme IdeS, which cleaves in the Fc hinge region. Altogether, 33 N-glycan structures were identified. The predominant glycoforms found on the Fc portion were G0, G1 and G2 (core hepatasaccharide with 0, 1 or 2 galactose residues). The percent G0 (48-55%), G1 (19-25%) and G2 (5-7%) structures were similar among the three products. The predominant glycoform on the TNFR portion is a sialylated species G2SA. GP2015 has slightly lower levels of this species (6.1 – 6.6%) relative to US-licensed Enbrel and EU-approved Enbrel (8.0 – 10.7% and 7.5 – 10.9%, respectively). However, the location of the N-glycan structures in TNFR2 does not interfere with TNF binding.

Small differences were noted in the levels of high mannose forms Man 5, Man 6 and Man8 (~2.2% for GP2015 and ~8% for US-licensed Enbrel and EU-approved Enbrel). High mannose glycan structures can alter the PK of a molecule though binding to cell surface mannose binding proteins. However, PK similarity was established for GP2015 and US-licensed Enbrel, which addresses the residual uncertainty in the differences in high mannose glycans between GP2015 and US-licensed Enbrel.

Other identified N-glycoforms on either the TNFR2 or Fc portion of the molecules were generally present at levels below 3% and were consistent among the GP2015, US-licensed Enbrel, and EU-approved Enbrel lots.

Process-related Substances and Impurities

The types and levels of process-related substances and impurities in the three products were assessed quantitatively by methods typically used by the biotechnology industry. Such substances originate from the complex biological culture system, (HCPs, DNA, and media components, etc.) or the purification process, (leachates from chromatography resins). The goal in bioprocessing is to remove these inevitable undesirable components of bioreactor cell culture to levels as low as achievable by the downstream purification. The three products all achieved acceptably low levels of residual impurities (data not shown).

Comparative Stability Studies

Sandoz evaluated comparative stability of GP2015, US-licensed Enbrel and EU-approved Enbrel in several stability studies including thermal stability at 25°C for 6 months and 40°C for 1.5 months and forced degradation studies using high and low pH, oxidizing conditions, exposure to light and mechanical stress. The products were evaluated for the accumulation of high and low molecular weight species (SE-HPLC and non-reducing CE-SDS), changes in hydrophobic variants (RP-HPLC), acidic variants (capillary zone electrophoresis), or loss of potency (TNF-α neutralization). The stability patterns of the three products were equivalent across all studies.

Conclusions on Analytical Similarity Assessment

In summary, the GP2015 product was evaluated and compared to US-licensed Enbrel, and EU-approved Enbrel in a battery of biochemical, biophysical and functional assays. The exercise also included assays that addressed each potential mechanism of action. The evidence submitted supports the conclusion that GP2015 is highly similar to US-licensed Enbrel. The amino acid sequences of GP2015 and US-licensed Enbrel are identical. A comparison of the secondary and tertiary structures, and the impurity profiles, of GP2015 and US-licensed Enbrel support the conclusion that the two products are highly similar. TNF-α binding and neutralization activities, reflecting the primary mechanism of action of US-licensed Enbrel are similar, supporting a conclusion that GP2015 has the same mechanism of action as US-licensed Enbrel.

Some tests indicate that subtle shifts in glycosylation (afucosylation and high mannose) exist and are likely an intrinsic property of the GP2015 product due to the manufacturing process. Afucosylation is associated with ADCC activity specifically through binding FcγRIIIa and high mannose glycans (which contribute to the total afucosylated glycoforms) can also impact PK. However, consistent with literature, GP2015 and the reference product have low ADCC activity relative to anti-TNF mAbs and another mAb

whose major MOA includes ADCC. In addition, the binding to FcγRIIIa by SPR was highly similar. The residual uncertainty of ~6% difference in high mannose forms was addressed by the PK similarity between GP2015 and US-licensed Enbrel, as discussed in the section on Clinical Pharmacology below. Thus, based on the extensive comparison of the functional, physicochemical, protein and higher order structure attributes, GP2015 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components. Further, the data submitted by Sandoz, support the conclusion that GP2015 and US-licensed Enbrel have the same mechanisms of action for specified indications, to the extent that the mechanisms of action are known or can reasonably be determined.

In addition, the three pairwise comparisons of GP2015, US-licensed Enbrel, and EU-approved Enbrel met the pre-specified criteria for analytical similarity. Sandoz provided a sufficiently robust analysis for the purposes of establishing the analytical component of the scientific bridge among the three products to justify the relevance of comparative data generated from clinical and non-clinical studies that used EU-approved Enbrel, to support a demonstration of biosimilarity of GP2015 to US-licensed Enbrel.

7 Pharmacology/Toxicology

Executive Summary

The GP2015 nonclinical development program was adequate to support clinical development. The pharmacology and toxicology studies submitted in support of the BLA included pharmacology studies in Tg197 mice (which constitutively express human TNFα and develop polyarthritis) comparing GP2015 vs. EU-approved Enbrel, pharmacokinetic studies in rabbits comparing GP2015 vs. EU-approved Enbrel, and a comparative 28-day repeat-dose toxicology study of GP2015 and EU-approved Enbrel in the cynomolgus monkey.

Collectively, there was no evidence in the aforementioned nonclinical studies to indicate potential safety concerns associated with GP2015 administration. The toxicokinetic profile of GP2015 was considered reasonably similar to that of EU-approved Enbrel in cynomolgus monkeys and rabbits. Further, the efficacy of GP2015 in Tg197 transgenic mice (i.e., reduced development of arthritis-related pathology) was similar to that of EU-approved Enbrel.

The nonclinical pharmacology, pharmacokinetic, and repeat-dose toxicity data submitted support a demonstration of the similarity (i.e., comparable achieved exposures, safety, and efficacy) between GP2015 and EU-approved Enbrel from the nonclinical Pharmacology and Toxicology perspective. There are no outstanding issues from the nonclinical Pharmacology and Toxicology perspective.

Conclusion

In summary, the animal studies submitted demonstrate the similarity of GP2015 to EU-approved Enbrel in terms of the pharmacologic, pharmacokinetic, and repeat-dose toxicity profiles. From the Pharmacology and Toxicology perspective, the results of these animal studies can be taken together with the data from the analytical bridging studies (refer to the CMC section for details) to support a demonstration that GP2015 is biosimilar to US-licensed Enbrel. No residual uncertainties have been identified by this discipline.

8 Clinical Pharmacology

Executive Summary

The clinical pharmacology program of GP2015 included three pharmacokinetic (PK) studies (Study 101, 102, and 104) in healthy subjects, a cross-study PK comparison between US-licensed Enbrel and EU-approved Enbrel from studies 101 and 102 (Report 105), and steady state PK assessment in patients with chronic PsO (Study 302).

Pharmacokinetic similarity was established between GP2015 and US-licensed Enbrel (Study 102). The clinical pharmacology program also provided PK bridging data, in addition to the analytical bridging data, to scientifically justify the relevance of the comparative data from the clinical development program with EU-approved Enbrel to support a demonstration of no clinically meaningful differences to US-licensed Enbrel. For additional considerations on the use of data generated using non-US-approved comparator product, refer to section 2, (under “The Reference Product”) above.

In addition, similar steady state PK was demonstrated between GP2015 and EU-approved Enbrel with repeat dosing in the setting of treatment of patients with plaque psoriasis in Study 302.

Overall, the GP2015 clinical pharmacology program supports the demonstration of PK similarity between GP2015 and US-licensed Enbrel, and the scientific bridge between GP2015, US-licensed Enbrel, and EU-approved Enbrel. The PK results add to the totality of evidence to support a demonstration of biosimilarity of GP2015 and US-licensed Enbrel.

Description of Relevant Clinical Pharmacology Studies

The clinical pharmacology program of GP2015 to evaluate the pharmacokinetic (PK) similarity between GP2015 and US-licensed Enbrel and to assess the PK element of the scientific bridge between GP2015, US-licensed Enbrel and EU-approved Enbrel included three PK studies (Studies 101, 102, and 104) in healthy subjects, a cross-study

PK comparison (Report 105), and steady state PK assessment in patients with chronic PsO (Study 302) (Table 12).

Table 12. Key Design Features of GP2015 Clinical Studies

Study ID	Design	Objectives	Subjects	Treatments	Endpoints
Clinical Pharmacology Studies					
Study 101	R, DB, 2-way cross-over	PK, safety, and immunogenicity	57 healthy subjects	SD 50 mg SC: • GP2015 • EU-Enbrel	C_{max}, AUC_t and AUC_{inf}
Study 102	R, DB, 2-way cross-over	PK, safety, and immunogenicity	54 healthy subjects	SD 50 mg SC: • GP2015 • US-Enbrel	C_{max}, AUC_t and AUC_{inf}
Study 104	R, DB, 2-way cross-over	PK, safety, and immunogenicity	54 healthy males	SD 50 mg SC: • GP2015 • EU-Enbrel	C_{max}, AUC_t and AUC_{inf}
Report 105	A cross-study comparison of studies 101 and 102				
Comparative Clinical Study					
Study 302	R, DB, PG TP1 (Wk 0-12)	Efficacy, safety, immunogenicity, PK	531 PsO patients	50 mg SC twice weekly: • GP2015 • EU-Enbrel	PASI 75
	R, DB, PG TP2 (switching) (Wk 12-30)	Safety, immunogenicity, PK	PsO patients re-randomized	50 mg SC Q weekly: • GP2015 cont • GP2015 switch • EU-Enbrel cont • EU-Enbrel switch	Safety, Immunogenicity

Each of the three PK studies was conducted as randomized, two-way crossover studies to assess PK, safety, and immunogenicity. In these studies, healthy subjects received one single dose of 50 mg subcutaneously (SC) of study drug followed by a washout period of at least 35 days and were then crossed over to receive another single dose of 50 mg SC of the comparator product. As described in the draft guidance for Industry entitled, "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product,"[12] a single-dose, randomized study is generally the preferred design for PK similarity assessments. A cross-over design is appropriate for etanercept because it has a relatively short half-life and low immune response rate. Additionally, conducting the study in healthy subjects is reasonable as it is more sensitive in

[12] Guidance for Industry "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product." May 2014. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf

evaluating the product similarity due to lack of potentially confounding factors such as underlying and/or concomitant disease and concomitant medications. The 50 mg SC dose is relevant as it is consistent with the approved dose of US-licensed Enbrel.

- Study 102 was the pivotal clinical pharmacology study designed to evaluate PK similarity, safety, and immunogenicity of GP2015 and US-licensed Enbrel.

- Both Study 101 and Study 104 were designed to compare the PK profiles of GP2015 and EU-approved Enbrel. Study 104 was conducted on request by the European Regulatory Authorities to support the demonstration of PK similarity of GP2015 to the EU-approved Enbrel, as in Study 101, the pre-specified acceptance criteria were met for C_{max} but not for AUC_{0-t} and AUC_{0-inf}.

- A pre-specified cross-study comparison was conducted to establish the PK bridge between US-licensed Enbrel (from Study 102) and EU-approved Enbrel (from Study 101) (Report 105). In addition to the analytical bridging data, the PK comparison provided in the report and the PK similarity data from Studies 101, 102, and 104 comprised the bridging data to scientifically justify the relevance of the comparative data from the clinical development program with EU-approved Enbrel. For additional considerations on the use of data generated using non-US-approved comparator product, refer to section 2, (under "The Reference Product") above. A cross-study comparison was justified because both Study 101 and 102 had identical study design, eligibility criteria, demographic and baseline characteristics of the study population, GP2015 product lot, and bioanalytical method. The two studies were performed during an overlapping time period.

- The supportive PK similarity assessment in the setting of repeat dosing was conducted in patients with moderate to severe chronic plaque-type psoriasis (Study 302). The Study 302 was designed as a multi-center, randomized, double-blind, parallel group, comparative clinical efficacy, safety, and immunogenicity study between GP2015 and EU-approved Enbrel. Sparse PK samples from 147 patients were collected for trough concentrations at Week 2, 4, 8, and 12.

The PK samples in the clinical pharmacology studies were analyzed with validated ELISA method. The bioanalytical assays used in the PK studies provided total protein concentration measurement and were not able to distinguish the disulfide bond correctly-bridged variant and wrongly-bridged variant. Of note, the Applicant submitted data from one additional PK study, Study 103, designed to assess PK similarity between two delivery devices following a single dose of GP2015. Because this study was not intended to assess similarity between GP2015 and the reference product, it is not discussed further in this briefing document.

Results of Clinical Pharmacology Studies

Study 102: GP2015 vs US-licensed Enbrel

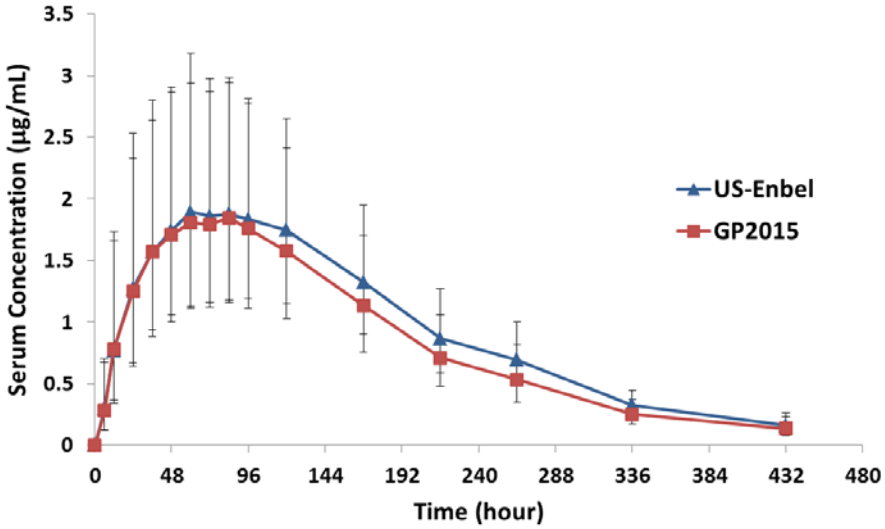
Study 102 was a single center, randomized, double-blind, two-way crossover study with two treatment periods comparing a single-dose 50 mg SC injection of the test product GP2015 and US-licensed Enbrel in 54 healthy subjects. The pairwise comparisons of GP2015 and US-licensed Enbrel met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}tlast}$, and C_{max} within the interval of 80% to 125%) as summarized in Table 13 and depicted in Figure 17. The analytical data on glycan structure showed small differences in the levels of high mannose forms Man 5, Man 6 and Man8 (~2.2% for GP2015 and ~8% for US-licensed Enbrel and EU-approved Enbrel). High mannose glycan structures may alter the PK of a molecule though binding to cell surface mannose binding proteins. However, PK similarity was demonstrated for GP2015 and US-licensed Enbrel, which addresses the residual uncertainty in the differences in high mannose glycans between GP2015 and US-licensed Enbrel and which supports a demonstration of biosimilarity between GP2015 and US-licensed Enbrel.

Table 13. Statistical Analysis of the PK Parameters of GP2015 and US-Licensed Enbrel in Study 102

Parameter	N	GP2015	US-Enbrel	Ratio (GP2015/US-Enbrel)[2]
$AUC_{0\text{-}t}$ (µg·h/mL)[1]	53	369.761	414.962	0.8911 (0.8308, 0.9557)
$AUC_{0\text{-}inf}$ (µg·h/mL)[1]	54	390.286	439.656	0.8877 (0.8320, 0.9471)
C_{max} (µg/mL)[1]	54	2.028	2.146	0.9450 (0.8695, 1.0271)

Source: FDA analysis of data from Sandoz 351(k) BLA submission
[1] Least-squares geometric means
[2] Ratio (90% CI)

Figure 17. Geometric Mean Serum Concentration-time Profiles of GP2015 (red, N=54) and US-licensed Enbrel (blue, N=54) from Study 102



Source: FDA analysis of data from Sandoz 351(k) BLA submission

Studies 101 and 104: GP2015 vs EU-approved Enbrel

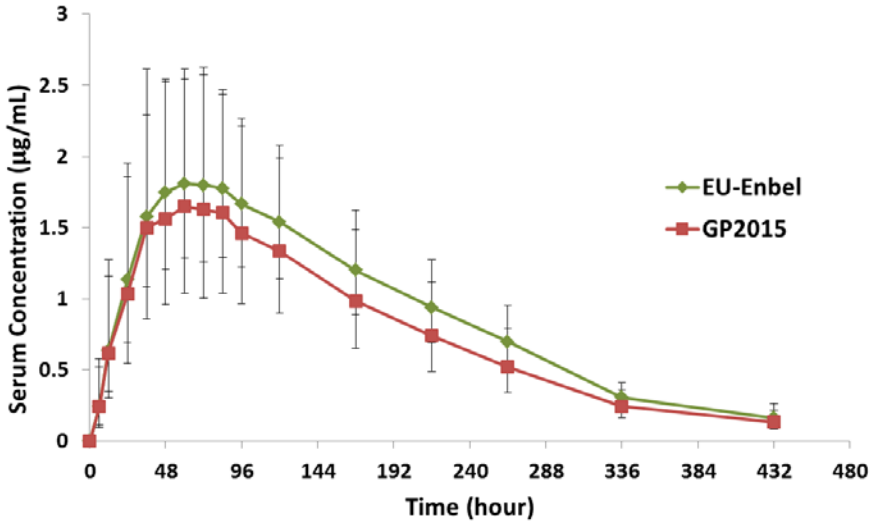
Study 101 was a single center, randomized, double-blind, two-way crossover study with two treatment periods comparing a single-dose 50 mg SC injection of the test product GP2015 and comparator EU-approved Enbrel in healthy subjects. The pairwise comparison of GP2015 and EU-approved Enbrel was within the pre-specified criteria for C_{max} but not for AUC_{0-t} and AUC_{0-inf} as summarized in Table 14 and depicted in Figure 18.

Table 14. Statistical Analysis of the PK Parameters of GP2015 and EU-approved Enbrel in Study 101

Parameter	N	GP2015	EU-Enbrel	Ratio (GP2015/EU-Enbrel)[2]
AUC_{0-t} (µg·h/mL)[1]	49	335.150	392.619	0.8536 (0.7830, 0.9307)
AUC_{0-inf} (µg·h/mL)[1]	49	353.338	416.506	0.8583 (0.7803, 0.9223)
C_{max} (µg/mL)[1]	50	1.808	1.982	0.9124 (0.8247, 1.0094)

Source: FDA analysis of data from Sandoz 351(k) BLA submission
[1] Least-squares geometric means
[2] Ratio (90% CI)

Figure 18. Geometric Mean Serum Concentration-Time Profiles of GP2015 (red, N=50) and EU-approved Enbrel (green, N=50) from Study 101



Source: FDA analysis of data from Sandoz 351(k) BLA submission

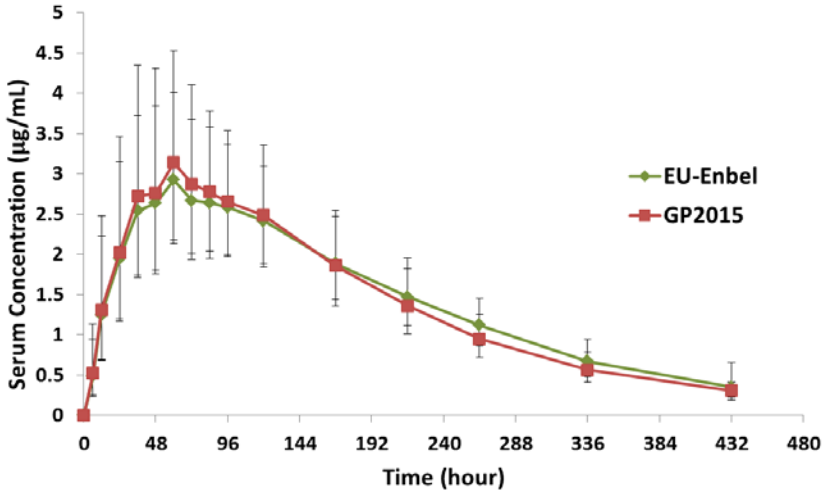
Study 104 was a single center, randomized, double-blind, two-way crossover study with two treatment periods comparing a single-dose 50 mg SC injection of the test product GP2015 and comparator EU-approved Enbrel in healthy males. It is a repeat study, on request by the European Regulatory Authorities, and has the same study design and methodology as Study 101. Notable differences include that only male subjects (n=54) were enrolled in Study 104 whereas both males (n=23) and females (n=23) were enrolled in the study 101; the batches of both GP2015 and EU-approved Enbrel were different between two studies; and the bioanalytical methods were different between two studies, although both methods were validated. The modifications implemented in Study 104 were intended to reduce the PK variability observed in Study 101. The pairwise comparisons of GP2015 and EU-approved Enbrel for AUC_{0-t}, AUC_{0-inf}, and C_{max} met the pre-specified acceptance criteria for PK similarity as summarized in Table 16 and depicted in Figure 19.

Table 15. Statistical Analysis of the PK Parameters of GP2015 and EU-approved Enbrel in Study 104

Parameter	N	GP2015	EU-Enbrel	Ratio (GP2015/EU-Enbrel)[2]
AUC_{0-t} (µg·h/mL)[1]	54	632.662	644.007	0.9824 (0.9449, 1.0214)
AUC_{0-inf} (µg·h/mL)[1]	54	680.945	706.883	0.9633 (0.9264, 1.0016)
C_{max} (µg/mL)[1]	54	3.416	3.087	1.1066 (1.0500, 1.1664)

Source: FDA analysis of data from Sandoz 351(k) BLA submission
[1] Least-squares geometric means
[2] Ratio (90% CI)

Figure 19. Geometric Mean Serum Concentration-time Profiles of GP2015 (red, N=54) and EU-approved Enbrel (green, N=54) from Study 104



Source: FDA analysis of data from Sandoz 351(k) BLA submission

The two-fold difference in exposure between Study 104 and Study 101 observed for GP2015 and EU-approved Enbrel could be due to different bioanalytical methods used in the two studies, however, other factors cannot be ruled out.

Report 105: EU-approved Enbrel and US-licensed Enbrel

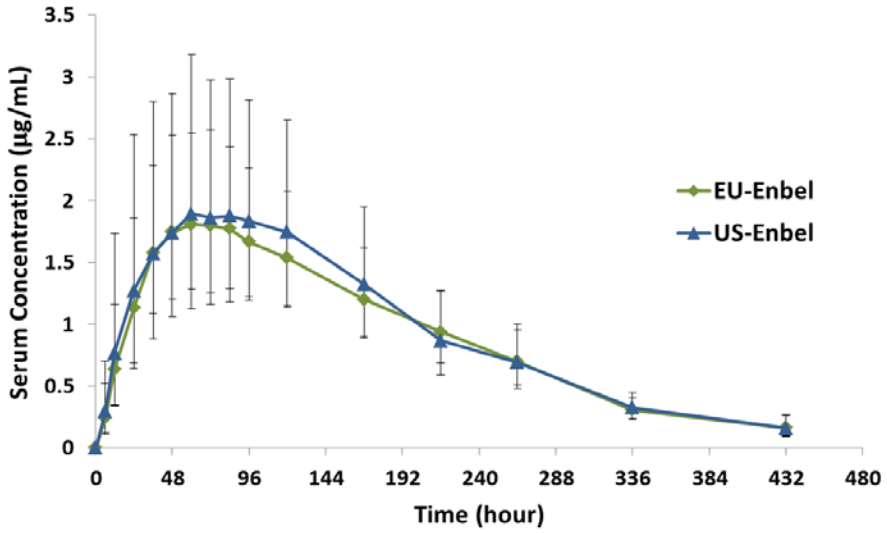
The PK comparison between EU-licensed Enbrel from study 101 and US-licensed Enbrel from Study 102 was conducted and summarized in Report 105. This statistical comparison was pre-defined and outlined as a pre-specified objective of both protocols. The sample size used in the data analysis was pre-determined from the two study protocols 101 and 102 and appears sufficient to assess biosimilarity between these two products. The pairwise comparisons of EU-approved Enbrel and US-licensed Enbrel met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of $AUC_{0\text{-inf}}$, $AUC_{0\text{-tlast}}$, and C_{max} within the interval of 80% to 125%) as summarized in Table 16 and depicted in Figure 20.

Table 16. Statistical Analysis of the PK Parameters of EU-approved Enbrel and US-Licensed Enbrel in Report 105

Parameter	EU-Enbrel	US-Enbrel	Ratio (EU-Enbrel/US-Enbrel)[2]
AUC_{0-t} (µg·h/mL)[1]	392.632 (N=49)	415.237 (N=53)	0.9456 (0.8397, 1.0647)
AUC_{0-inf} (µg·h/mL)[1]	416.484 (N=49)	439.738 (N=54)	0.9471 (0.8451, 1.0615)
C_{max} (µg/mL)[1]	1.980 (N=50)	2.146 (N=54)	0.9222 (0.8026, 1.0596)

Source: FDA analysis of data from Sandoz 351(k) BLA submission
[1] Least-squares geometric means
[2] Ratio (90% CI)

Figure 20. Geometric Mean Serum Concentration-time Profiles of EU-approved Enbrel (green, N=50) and US-licensed Enbrel (blue, N=54) from Report 105

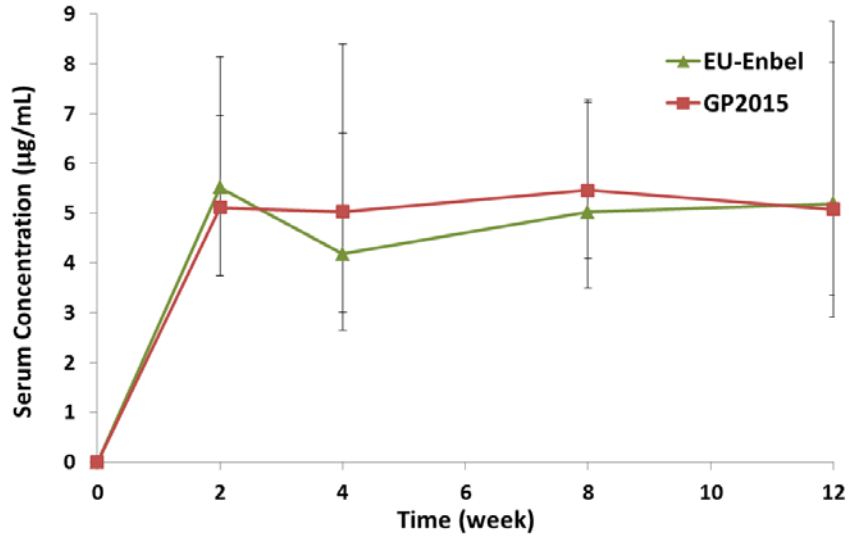


Source: FDA analysis of data from Sandoz 351(k) BLA submission

Study 302: Supportive PK in patients after repeat dosing

In comparative clinical Study 302, pre-dose PK samples were collected from 147 patients at Day 1, and at Weeks 2, 4, 8, and 12 during treatment period 1. The mean trough serum concentrations were generally comparable at each time point between GP2015 and EU-approved Enbrel at steady state. The mean serum trough concentrations-time profiles indicate steady-state was reached from Week 2 for GP2015 and EU-approved Enbrel (Figure 21).

Figure 21. Geometric Mean Trough Serum Concentration-time Profiles of GP2015 (red, N=72) and EU-approved Enbrel (green, N=75) from Study 302



Source: FDA analysis of data from Sandoz 351(k) BLA submission

Extrapolation of the PK Data for GP2015

The pharmacokinetic parameters of etanercept in patients with PsO were similar to those seen in patients with RA.[16] The estimated half-life of etanercept was about 100 hours and comparable in healthy subjects, JIA and RA patients. As a fusion glycoprotein and consisting entirely of human protein components, etanercept is expected to undergo proteolysis in patients across different diseases. There are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between GP2015 and US-licensed Enbrel in the indications sought for licensure. Since similar PK was demonstrated between GP2015 and US-licensed Enbrel in healthy subjects and psoriasis, a similar PK profile would be expected between GP2015 and US-licensed Enbrel in patients with RA, JIA, AS, and PsA.

Clinical Pharmacology Summary

Overall, the submitted clinical pharmacology studies are adequate to:

1) Demonstrate similarity of exposure between GP2015 and US-licensed Enbrel. The PK studies, conducted in healthy subjects, are considered sensitive to detect clinically significant differences in exposure among the products. Single-dose PK similarity pre-specified margins were met in comparison of GP2015 to US-licensed Enbrel, GP2015 to EU-approved Enbrel, and US-licensed Enbrel to EU-

[16] FDA-approved Enbrel labeling

approved Enbrel. The demonstration of similar exposure supports a finding of biosimiliarity between GP2015 and US-licensed Enbrel.

2) Establish the PK component of the scientific bridge to justify the relevance of the comparative data generated using EU-approved Enbrel to support a demonstration of the biosimilarity of GP2015 to US-licensed Enbrel.

3) Together with the analytical similarity (discussed in the CMC section above), justify the relevance of the PK findings from the GP2015 clinical program to the indications that were not directly studied in the GP2015 clinical program, for which US-licensed Enbrel is licensed and for which the Applicant is seeking licensure.

In summary, the PK similarity has been demonstrated between GP2015 and US-licensed Enbrel, and the results from the PK studies add to the totality of evidence to support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel. The PK studies have not raised any new uncertainties in the assessment of biosimilarity of GP2015 to US-licensed Enbrel.

9 Clinical Outcomes

Executive Summary

Sandoz Inc. submitted one comparative clinical study in patients with plaque psoriasis (Study 302). Of note, the comparative clinical efficacy data are derived from a clinical study using EU-approved Enbrel as the comparator. However, Sandoz has provided sufficient analytical and clinical PK bridging data (Studies 101, 102, and 104, and Report 105, discussed in the section on Clinical Pharmacology above) between GP2015, US-licensed Enbrel, and EU-approved Enbrel. These data justify the relevance of the comparative data generated using EU-approved Enbrel to support a demonstration of no clinically meaningful differences between GP2015 to US-licensed Enbrel.

Study 302 is a randomized, double blind comparative clinical study of GP2015 and EU-approved Enbrel in subjects age 18 years and older with chronic moderate-to-severe plaque psoriasis. Of the 531 subjects enrolled, 264 were randomized to the GP2015 arm and 267 randomized to the EU-approved Enbrel arm. The study provided data on subjects who underwent a transition from EU-approved Enbrel to GP2015 after Week 12. Subjects were enrolled in 12 countries, mostly in Eastern Europe.

The primary endpoint was the proportion of subjects at Week 12 achieving at least a 75% reduction from baseline in the Psoriasis Area Severity Index (PASI 75). The proportion of subjects achieving PASI 75 at Week 12 was similar in both the GP2015 and EU-approved Enbrel arms (70.5% vs. 71.5% in the full analysis population; the

exact 90% confidence interval for the difference was (-8.3, 6.0)). The confidence interval was within the pre-specified margin of ± 18%. The results of the supportive endpoints (mean percent change in PASI and the Investigator's Global Assessment) were consistent with the results of the primary endpoint.

The enrolled population in Study 302 was comparable to the populations enrolled in two historical placebo-controlled trials of Enbrel: Leonardi (2003)[17] and Papp (2005)[18]. One notable difference was the geographic location: the historical Enbrel studies were conducted in the US, Canada, and Western Europe, while Study 302 was conducted in Europe and South Africa, with most centers in Eastern Europe. The PASI 75 response rates in Study 302 were higher than in the historical studies (71.5% vs. 49%). While differences in the populations between the geographic locations could have contributed to the higher response rate in Study 302, that higher rate does not represent a loss of efficacy relative to the historical studies and does not negatively impact the assay sensitivity of the study. Further, we did not identify issues with the quality of study conduct or the integrity of the study data.

The safety analysis of the GP2015 clinical program in the plaque psoriasis study and in healthy subjects has not identified new safety signals compared to the known adverse event profile of US-licensed Enbrel. Further, the single transition from EU-approved Enbrel to GP2015 during TP2 of the study did not result in an increase in adverse events or immunogenicity, supporting the safety of the clinical scenario where non-treatment naïve patients transition to GP2015.

The FDA review of the safety, immunogenicity, and efficacy data from the comparative clinical study in patients with plaque psoriasis supports a demonstration that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel in the studied indication.

Clinical Outcomes Review

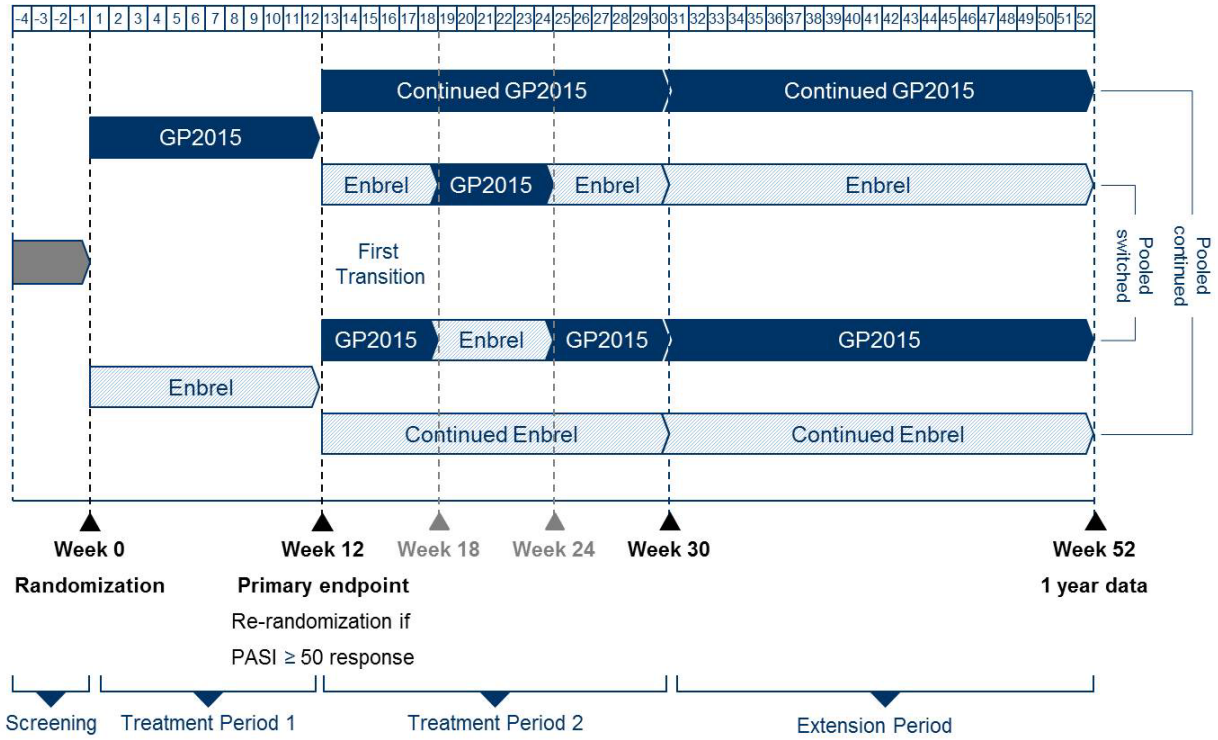
Study Design

Study 302 is a comparative clinical study in 531 subjects with clinically stable chronic plaque psoriasis involving at least 10% body surface area (BSA), i.e. PASI≥10, and Investigator's Global Assessment (IGA) ≥3. Subjects must have previously received phototherapy or systemic therapy or were candidates for such therapy in the opinion of the investigator. Of the 531 subjects enrolled, 264 were randomized to the GP2015 arm and 267 randomized to the EU-approved Enbrel arm. Subjects were enrolled at 71 centers in 12 countries (mostly in Eastern Europe). Subjects received a subcutaneous injection of 50 mg twice weekly for the first 12 weeks followed by 50 mg once weekly

[17] Leonardi CL et al, N Engl J of Med. 2003; 349:2014-22.
[18] Papp KA et al, Br J of Dermatol. 2005; 152:1304-12.

thereafter. The study included three treatment periods summarized in Figure 22. In treatment period 1, TP1 (baseline to Week 12), subjects were randomized to GP2015 or EU-approved Enbrel. In treatment period 2, TP2 (Week 12 to Week 30), subjects with at least a 50% reduction in PASI at Week 12 were randomized to maintain their initially randomized treatment or undergo pre-defined switches between the two treatments at 6-week intervals. In the extension period (Week 30 to 52), subjects maintained the last assigned treatment through Week 52. This application provided data for all subjects who completed TP1 and TP2.

Figure 22. Schemata of Study 302 Design



Source: Figure is an excerpt from Sandoz 351(k) BLA submission

Brief Description of Efficacy Endpoints

The primary endpoint was PASI 75 at Week 12. The PASI score is derived from assessments for erythema, plaque elevation, and scaling over four body regions (head, trunk, upper limbs, and lower limbs). PASI scores can range from 0 to 72. PASI 75 is defined as at least a 75% reduction from baseline in the PASI score. The key secondary endpoint was percent change in PASI averaged across TP1. Additional secondary endpoints included percent change in PASI at each visit and IGA success (clear or almost clear) at each visit.

The protocol stated that the difference in PASI 75 response at Week 12 between GP2015 and EU-approved Enbrel would be analyzed with an exact 95% confidence interval. For comparative clinical studies, FDA has recommended analyses using 90% confidence intervals.

The randomization in Study 302 was stratified by prior systemic psoriasis therapy and weight. The protocol stated that the PASI 75 endpoint would be evaluated with exact confidence intervals (not adjusted for covariates); however, the statistical analysis plan stated that the endpoint would be analyzed with a confidence interval adjusted for the stratification factors (body weight and prior therapy classifications). Although the Applicant's primary analysis in the statistical analysis plan used a model adjusted for the stratification factors, because of the variability of capturing the prior systemic therapy, FDA focused on the analysis proposed in the original protocol (exact confidence intervals) which did not use adjustment based on the stratification factors. A consistent similarity in clinical outcomes between GP2015 and EU-approved Enbrel was demonstrated using both approaches.

Discussion on Similarity Margin

The pre-specified similarity margin for the difference in proportions was ±18%. The Applicant justified the choice of an 18% similarity margin noting that 18% maintains 60% of the observed treatment effects relative to placebo (45-46%) reported in Leonardi (2003)[19] (49% for Enbrel vs. 4% for placebo) and Papp (2005)[20] (49% for Enbrel vs. 3% for placebo). Under the design characteristics used by the Applicant (proposed sample size of approximately 546 subjects with an expected PASI 75 response rate of 49%), a 90% confidence interval would be the point estimate for the treatment difference plus or minus approximately 7%[21]. Thus, the observed point estimate for the treatment difference could be approximately ±10% under these design assumptions and still be within the pre-specified margin of 18%.

Study Conduct

Treatment groups in the studies were generally balanced with respect to demographics and baseline characteristics. The study was conducted in Europe and South Africa with most enrollments in Eastern Europe. None of the study sites were in the US. The average baseline disease PASI score was 22.5, average BSA was 30.7 and 71% of subjects had moderate and 29% severe disability on the IGA, consistent with the intended population of patients with moderate-to-severe chronic plaque psoriasis.

[19] Leonardi CL et al, N Engl J of Med. 2003; 349:2014-22.
[20] Papp KA et al, Br J of Dermatol. 2005; 152:1304-12.
[21] Normal approximation to the binomial: $\pm 1.645\sqrt{2(0.49)(0.51)/273}$

Study 302 randomized 531 subjects: 264 to GP2015 and 267 to EU-approved Enbrel. The discontinuation rate prior to Week 12 was low (see Table 17); 3% of GP2015 and 4.5% of EU-approved Enbrel subjects withdrew. The most common reason for study discontinuation was 'subject decision.' A greater number of EU-approved Enbrel subjects than GP2015 subjects (1.9% vs. 0.8%) discontinued due to subject decision. Similar numbers of subjects withdrew due to adverse events.

Table 17. Patient Disposition in Treatment Period 1 (Week 1-12), Study 302

	GP2015	EU-Enbrel
Subjects Randomized	264	267
Discontinued Treatment Period 1	8 (3.0%)	12 (4.5%)
Adverse event	4 (1.5%)	3 (1.1%)
Death	--	1 (0.4%)
Lost to follow-up	1 (0.4%)	--
Non-compliance with study treatment	--	1 (0.4%)
Physician decision	--	1 (0.4%)
Protocol deviation	1 (0.4%)	--
Subject decision	2 (0.8%)	5 (1.9%)
Injection site reaction	--	1 (0.4%)

Source: FDA analysis of data from Sandoz 351(k) BLA submission

Most subjects (94%) who enrolled in the study continued on to TP 2 (Weeks 12 through 30). The most common reasons for discontinuation in TP 2 were subject decision and adverse events.

Approximately 10% of subjects on each treatment arm were excluded from the per protocol population. The reasons for exclusion were reasonably balanced across the treatment arms. The most common reasons for exclusion were not completing TP 1 and having the visit more than 6 days from the planned Week 12 visit day (visit window exclusion).

The randomization in Study 302 was stratified on prior systemic psoriasis therapy and weight. The Agency investigated why so many of the stratification values entered by the investigators into the randomization system did not match the data recorded about prior therapies. It was determined that the protocol did not provide sufficient guidance to the individual investigators on what types of therapies were to be considered prior systemic therapies for psoriasis or what time frame should be used to determine if prior therapies had been used. The sensitivity analyses to account for the differences in adequately capturing and classifying prior systemic psoriatic therapies were consistent with the primary analyses and did not impact the conclusions of the study. No other significant issues with study conduct were identified.

Study Results

Study 302 met the similarity criteria for the primary endpoint of PASI 75 at Week 12 in both the full analysis set and the per protocol population. The exact confidence intervals for the difference in PASI 75 response were within the pre-specified similarity margin of ±18% (see Table 18). Because of the concerns with how the prior therapy information was collected for the stratification and randomization, FDA recommends presenting the results using the analysis specified in the protocol (exact confidence intervals) rather than using the analysis specified in the statistical analysis plan (confidence intervals based on a logistic regression model with terms for body weight and prior therapy). For the full analysis population (FAS), missing data was imputed as non-response. Because only 4% of subjects had missing data at Week 12, even when subjects with missing data are handled in opposite ways (such as all successes on one arm and as all failures on the other) it does not change the conclusion for similarity.

Table 18. Exact Confidence Intervals for the Risk Difference of PASI 75 Response Rates, Study 302

Population	GP2015	EU-approved Enbrel	Difference	90% Conf. Int.
FAS	70.5% (n=264)	71.5% (n=267)	-1.1%	(-8.3%, 6.0%)
PPS	73.6% (n=239)	75.5% (n=241)	-1.9%	(-9.4%, 5.6%)

Source: FDA analysis of data from Sandoz's 351(k) BLA submission
FAS = full analysis set (missing data imputed as non-response), PPS = per protocol set

In addition, the results of the analyses using the various definitions of the prior therapy classification (the ones used in the randomization stratification, and the re-classified 'actual' results used in the Week 12 and Week 30 study reports) lead to similar results as the exact confidence interval (see Table 19).

Table 19. Analyses Using Various Prior Therapy Variable Definitions (FAS), Study 302

	GP2015 N=264	EU-approved Enbrel N=267	Difference	90% Conf. Int.
Stratification classification	70.4%	71.6%	-1.1%	(-7.5%, 5.3%)
Week 12 Report 'actual' classification	70.3%	71.7%	-1.4%	(-7.7%, 5.0%)
Week 30 Report 'actual' classification	70.4%	71.6%	-1.2%	(-7.5%, 5.2%)

Source: FDA analysis of data from Sandoz's 351(k) BLA submission
Note: Confidence intervals computed using a logistic regression model with terms for treatment group, body weight classification (<90 kg, ≥ 90 kg), and prior systemic therapy classification (no or any)

The results for the secondary endpoints of percent change in PASI at Week 12 and IGA success (clear or almost clear) were consistent with the primary endpoint. The mean percent change in PASI at Week 12 was -82.6% for GP2015 and -81.7% for EU-approved Enbrel. The proportion of IGA responders was 58.2% for GP2015 and 55.1% for EU-approved Enbrel.

Assay Sensitivity and the Constancy Assumption

To reliably evaluate whether there are clinically meaningful differences between two products, a comparative clinical study must have assay sensitivity, or the ability to detect meaningful differences between the products, if such differences exist. In addition, to reliably evaluate whether the experimental treatment retains a certain proportion of the effect of the comparator versus placebo, the constancy assumption must be reasonable. The constancy assumption assumes that estimates of the effect of the comparator from historical, placebo-controlled trials are unbiased for the setting of the comparative clinical study. Historical studies of US-licensed Enbrel (Leonardi (2003) and Papp (2005)) reported Week 12 PASI 75 response rates for Enbrel of approximately 49% versus 3-4% for placebo. In contrast, in Study 302 the Week 12 PASI 75 response rate for EU-approved Enbrel was 71.5%. The disease-related inclusion criteria were similar across both the historical studies and Study 302 (PASI ≥ 10, BSA ≥ 10%, subjects have had or were candidates for prior phototherapy or systemic therapy; Study 302 also required subjects to have IGA ≥ 3). In contrast to historical studies, Study 302 allowed enrollment of subjects who have had prior use of a TNF-α inhibitor; however only 7/531 subjects in Study 302 reported using prior TNF-α inhibitors. The other major difference between Study 302 and the historical studies was geographic location: the previous studies were conducted in the US, Canada, and Western Europe, while Study 302 was conducted in Europe and South Africa, with most centers in eastern Europe. While this is acceptable for a comparative clinical study, it could have been a contributing factor to the relatively high overall response rates in Study 302. The response rate in Study 302 is at least as high as that observed in the historical studies, and thus does not represent a loss of efficacy relative to the historical studies and does not negatively impact the assay sensitivity of the study.

In summary, the Applicant has provided statistically robust comparative efficacy data demonstrating similar efficacy between GP2015 and EU-approved Enbrel in patients with moderate-to-severe plaque psoriasis. The primary analysis was supported by the analysis of key secondary endpoints and sensitivity analyses accounting for the missing data. The results from the GP2015 clinical program support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel in the indication studied.

Analysis of Safety in GP2015 Clinical Program

Adequacy of the safety database

The comparative safety and immunogenicity data with repeat dosing were derived from the single comparative clinical study in plaque psoriasis (Study 302). The safety population included 531 subjects, of whom 143 (95.3%) were exposed to GP2015 for at least 24 weeks. Patients with plaque psoriasis received 50 mg SC twice weekly for the first 12 weeks, then 50 mg SC weekly up to 52 weeks of GP2015 or EU-approved Enbrel. Additional safety and immunogenicity data with single dosing were provided from the PK studies 101, 102, and 104.

Note that the majority of the safety data are derived from clinical studies using the EU-approved Enbrel. However, Sandoz has provided comparative analytical data and clinical PK bridging data between the US-licensed and EU-approved Enbrel to justify the relevance of comparative data, including safety data generated using EU-approved Enbrel to support a demonstration of no clinically meaningful differences between the GP2015 and US-licensed Enbrel.

Overview of Safety

In the GP2015 clinical program, the overall incidences of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and AEs leading to discontinuation or treatment interruption, infections, injection site reactions, were similar between GP2015 and the comparator products. The incidence of adverse events, serious adverse events, adverse events of special interest, and death in the comparative clinical study 302 in patients with plaque psoriasis are summarized in Table 20. No new safety signals were identified in the GP2015 group compared to the known adverse event profile of US-licensed Enbrel.

Table 20. Summary of Adverse Events in Treatment Periods 1 and 2 Through Week 30, Study 302

	Treatment Period 1		Treatment Period 2			
Number of patients with:	GP2015 N=264 n (%)	EU-Enbrel N=267 n (%)	Cont GP2015 N=150 n (%)	Cont EU-Enbrel N=151 n (%)	Switched EU-Enbrel N=96 n (%)	Switched GP2015 N=100 n (%)
At least 1 TEAE	99 (38)	96 (36)	47(31)	52 (34)	35 (37)	32 (32)
Serious Adverse Events	4 (2)	3 (1)	1 (<1)	2 (1)	3 (3)	3 (3)
Discontinuation due to AE	5 (2)	4 (2)	1 (<1)	2 (1)	5 (5)	1 (1)
Treatment interruption due to AE	3 (1)	6 (2)	6 (4)	6 (4)	2 (2)	3 (3)
Deaths	--	1 (0.4)	--	--	--	--
AESI	9 (3)	5 (2)	7 (5)	3(2)	2 (2)	3 (3)

Continued GP2015: GP2015 continued from Period 1
Continued Enbrel: EU-Enbrel continued from Period 2
Switched GP2015: Switched to treatment sequence EU-Enbrel>GP2015>EU-Enbrel in Period 2
Switched Enbrel: Switched to treatment sequence GP2015>EU-Enbrel>GP2015 in Period 2
Patients experiencing multiple events are counted once within each treatment group
Source: FDA analysis of data from Sandoz's 351(k) BLA submission

Death

A single death occurred in the EU-approved Enbrel treatment group. This 58 year old Caucasian male subject who had concomitant conditions that included diabetes and hypertension, died of cardiopulmonary failure not suspected related to the study drug. There were no other deaths in the GP2015 clinical program.

Nonfatal Serious Adverse Events (SAE)

The proportion of patients who experienced at least one SAE was similar between the two treatment groups, GP2015 and EU-approved Enbrel, during treatment period 1 in Study 302 (Table 21). There was no notable difference in the incidence of SAEs in those patients who underwent a transition from EU-approved Enbrel to GP2015 as compared to those who continued on EU-approved Enbrel, nor in those that continued on GP2015 and those that transitioned from GP2015 to EU- approved Enbrel in treatment period 2 (Table 21). The types of SAE did not identify any new safety concerns. None of the SAEs were reported in more than one patient.

Table 21. Serious Adverse Events in Treatment Periods 1 and 2 Through Week 30, Study 302

	Treatment Period 1		Treatment Period 2			
System organ class Preferred term	**GP2015 N=264 n(%)**	**EU-Enbrel N=267 n(%)**	**Cont GP2015 N=150 n (%)**	**Cont EU-Enbrel N=151 n (%)**	**Switched EU-Enbrel N=96 n (%)**	**Switched GP2015 N=100 n (%)**
Number of patients with SAEs	**4 (1.5)**	**3 (1.1)**	**1 (0.7)**	**2 (1.3)**	**3 (3.1)**	**3 (3.0)**
Cardiac disorders	**0**	**1 (0.4)**				
Cardiopulmonary failure[1]	0	1 (0.4)				
Eye disorders	**0**	**1 (0.4)**				
Retinal detachment	0	1 (0.4)				
Gastrointestinal disorders			**0**	**0**	**0**	**1 (1.0)**
Umbilical hernia			0	0	0	1 (1.0)
Hepatobiliary disorders	**0**	**1 (0.4)**	**0**	**0**	**0**	**1 (1.0)**
Cholelithiasis			0	0	0	1 (1.0)
Drug-induced liver injury	0	1 (0.4)				
Immune system disorders	**1 (0.4)**	**0**				
Milk allergy	1 (0.4)	0				
Infections and infestations	**1 (0.4)**	**0**	**0**	**1 (0.7)**	**2 (2.1)**	**0**
Appendicitis	1 (0.4)	0				
Diverticulitis			0	0	1 (1.0)	0
Pneumonia			0	1 (0.7)	0	0
Tonsillitis			0	0	1 (1.0)	0
Injury, poisoning, and procedural complications	**1 (0.4)**	**0**	**1 (0.7)**	**1 (0.7)**	**0**	**0**
Lower limb fracture	1 (0.4)	0				
Meniscus injury			1 (0.7)	0	0	0
Upper limb fracture			0	1 (0.7)	0	0
Musculoskeletal and connective tissue disorders			**0**	**0**	**0**	**1 (1.0)**
Psoriatic arthropathy			0	0	0	1 (1.0)
Neoplasms benign, malignant, and unspecified	**1 (0.4)**	**0**				
Malignant melanoma in situ	1 (0.4)	0				
Respiratory, thoracic, and mediastinal disorders			**0**	**0**	**1 (1.0)**	**0**
Pulmonary sarcoidosis			0	0	1 (1.0)	0
Skin and subcutaneous tissue disorders			**0**	**0**	**0**	**1 (1.0)**
Psoriasis			0	0	0	1 (1.0)

Continued GP2015: GP2015 continued from Period 1
Continued Enbrel: EU-Enbrel continued from Period 2
Switched GP2015: Switched to treatment sequence EU-Enbrel>GP2015>EU-Enbrel in Period 2
Switched Enbrel: Switched to treatment sequence GP2015>EU-Enbrel>GP2015 in Period 2
Patients experiencing multiple events within the same SOC and PT are counted once under those categories and total row
Source: FDA analysis of data from Sandoz's 351(k) BLA submission

Discontinuations due to Adverse Events

Adverse events leading to discontinuation were rare overall and did not cluster within any specific system organ class (SOC). The proportion of patients discontinuing due to

an adverse event was similar between the GP2015 and EU-approved Enbrel treatment groups in treatment period 1 and did not appear to increase in treatment period 2 following the transition from EU-approved Enbrel to GP2015 as detailed in Table 22.

Table 22. TEAEs Leading to Study Drug Discontinuation in Treatment Periods 1 and 2 through Week 30, Study 302

	Treatment Period 1		Treatment Period 2			
System organ class Preferred term	**GP2015 N=264 n (%)**	**EU-Enbrel N=267 n (%)**	**Cont GP2015 N=150 n (%)**	**Cont EU-Enbrel N=151 n (%)**	**Switched EU-Enbrel N=96 n (%)**	**Switched GP2015 N=100 n (%)**
Number of patients with TEAEs	**5 (1.9)**	**4 (1.5)**	**1 (0.7)**	**2 (1.3)**	**5 (5.2)**	**1 (1.0)**
Blood and lymphatic system disorders			**1 (0.7)**	**0**	**1 (1.0)**	**0**
Lymphadenopathy mediastinal			0	0	1 (1.0)	0
Thrombocytopenia			1 (0.7)	0		
Gastrointestinal disorders	**1 (0.4)**	**1 (0.4)**				
Abdominal distention	1 (0.4)	0				
Colitis ulcerative	0	1 (0.4)				
Immune system disorders			**0**	**1 (0.7)**	**0**	**0**
Hypersensitivity			0	1 (0.7)	0	0
Investigations	**2 (0.8)**	**1 (0.4)**				
Alanine aminotransferase	0	1 (0.4)				
Transaminases increased	1 (0.4)	0				
White blood cell decreased	1 (0.4)	0				
Cardiac disorders	**0**	**1 (0.4)**				
Cardiopulmonary failure[1]	0	1 (0.4)				
Hepatobiliary disorders	**0**	**1 (0.4)**				
Drug-induced liver injury[2]	0	1 (0.4)				
Hepatic steatosis			0	0	1 (1.0)	0
Neoplasms benign, malignant, and unspecified	**1 (0.4)**	**0**				
Malignant melanoma in situ[3]	1 (0.4)	0				
Psychiatric disorders			**0**	**0**	**2 (2.1)**	**0**
Drug abuse			0	0	1 (1.0)	0
Panic attack			0	0	1 (1.0)	0
Skin and subcutaneous tissue disorders	**1 (0.4)**	**0**	**0**	**1 (0.7)**	**1 (1.0)**	**1 (1.0)**
Dermatitis psoriasiform			0	0	0	1 (1.0)
Psoriasis			0	1 (0.7)	0	0
Pustular psoriasis	1 (0.4)	0	0	0	1 (1.0)	0

Continued GP2015: GP2015 continued from Period 1
Continued Enbrel: EU-Enbrel continued from Period 2
Switched GP2015: Switched to treatment sequence EU-Enbrel>GP2015>EU-Enbrel in Period 2
Switched Enbrel: Switched to treatment sequence GP2015>EU-Enbrel>GP2015 in Period 2
TEAE= treatment emergent adverse event; SAE= serious adverse event
[1] SAE leading to death
[2] SAE suspected to be related to drug
[3] SAE not suspected to be related to drug
Source: FDA analysis of data from Sandoz's 351(k) BLA submission

Adverse Events of Special Interest (AESI)

AESI were defined by preferred terms encompassing all of the special warnings and precautions given on the label for Enbrel. These included infections, serious infections, pneumonia, tuberculosis (TB), injection site reactions, anaphylaxis, congestive heart failure (CHF), serious hepatobiliary events, drug induced liver injury, malignancy and lymphoma, among other events.

Table 23 lists the observed TEAEs of special interest in treatment periods 1 and 2 by SOC and preferred term. A similar proportion of patients in both treatment groups reported TEAEs of special interest; 9 subjects (3.4%) and 5 subjects (1.9%) in the GP2015 and EU-approved Enbrel treatment groups had at least one TEAE of special interest, respectively in treatment period 1. A higher proportion of patients in the GP2015 treatment group (5 patients (1.9%) experienced AESI in the neoplasms benign, malignant, and unspecified (incl cysts and polyps) SOC as compared with the EU-approved Enbrel treatment group (1 patient (0.4%). The reported neoplasms were of varied types and reported early in treatment, and thus, not attributed to study treatment. The single malignant event was a malignant melanoma that was resected prior to initiation of study treatment.

In treatment period 2, a similar proportion of patients in the continued GP2015, continued EU-approved Enbrel, switched EU-approved Enbrel, and switched GP2015 treatment groups reported AESI (7 patients (4.7%), 3 patients (2.0%), 2 patients (2.1%), and 3 patients (3.0%) respectively). The most commonly affected SOCs were infections and infestations and skin and subcutaneous tissue disorders. One patient in the continued GP2015 group reported a melanocytic nevus in the neoplasms benign, malignant, and unspecified (incl cysts and polyps) SOC; this was the only reported AESI in this SOC in treatment period 2. Analysis of the safety data of patients who underwent a transition from EU-approved Enbrel to GP2015, as compared to those who continued treatment with EU-approved Enbrel did not reveal any increase in adverse events.

Table 23. Adverse Events of Special Interest in Treatment Periods 1 and 2 Through Week 30, Study 302

	Treatment Period 1		Treatment Period 2			
System organ class Preferred term	**GP2015 N=264 n (%)**	**EU-Enbrel N=267 n (%)**	**Cont GP2015 N=150 n (%)**	**Cont EU-Enbrel N=151 n (%)**	**Switched EU-Enbrel N=96 n (%)**	**Switched GP2015 N=100 n (%)**
Number of patients with at least one TEAE	**9 (3.4)**	**5 (1.9)**	**7 (4.7)**	**3 (2.0)**	**2 (2.1)**	**3 (3.0)**
Blood and lymphatic system disorders			**2 (1.3)**	**0**	**0**	**0**
Neutropenia			1 (0.7)	0		
Thrombocytopenia			1 (0.7)	0		
Infections and infestations	**3 (1.1)**	**3 (1.1)**	**4 (2.7)**	**0**	**2 (2.1)**	**1 (1.0)**
Blastomycosis			1 (0.7)	0	0	0
Oral candidiasis			1 (0.7)	0	0	0
Oral herpes	1 (0.4)	2 (0.7)				
Herpes simplex	1 (0.4)	1 (0.4)	1 (0.7)	0	0	1 (1.0)
Herpes zoster			0	0	1 (1.0)	0
Tinea infection	1 (0.4)	0	1 (0.7)	0	0	0
Tinea versicolour			0	0	1 (1.0)	0
Neoplasms benign, malignant, and unspecified	**5 (1.9)**	**1 (0.4)**	**1 (0.7)**	**0**	**0**	**0**
Skin papilloma	1 (0.4)	1 (0.4)				
Colon neoplasm[1]	1 (0.4)	0				
Lipoma	1 (0.4)	0				
Malignant melanoma in situ[2]	1 (0.4)	0				
Melanocytic nevus	1 (0.4)	0	1 (0.7)	0	0	0
Immune system disorders	**1 (0.4)**	**0**	**0**	**1 (0.7)**	**0**	**0**
Hypersensitivity	1 (0.4)	0	0	1 (0.7)	0	0
Investigations	1 (0.4)	0				
White blood cell decr	1 (0.4)	0				
Skin and subcut. tissue disorders	**0**	**1 (0.4)**	**0**	**2 (1.3)**	**0**	**2 (2.0)**
Rash			0	1 (0.7)	0	0
Rash generalized			0	0	0	1 (1.0)
Swelling face	0	1 (0.4)				
Urticaria			0	1 (0.7)	0	1 (1.0)

Continued GP2015: GP2015 continued from Period 1
Continued Enbrel: EU-Enbrel continued from Period 2
Switched GP2015: Switched to treatment sequence EU-Enbrel>GP2015>EU-Enbrel in Period 2
Switched Enbrel: Switched to treatment sequence GP2015>EU-Enbrel>GP2015 in Period 2
[1] tubular-villous adenoma with low grade dysplasia
[2] severe unrelated SAE the histological results were communicated after start of drug, but the diagnostic melanocytic nevus excision was done during screening, which resulted in study discontinuation.
Source: FDA analysis of data from Sandoz's 351(k) BLA submission

Common AEs

Adverse events in the Infections and Infestations SOC were the most common adverse events in the GP2015 development program with event rates similar between GP2015 and the comparator products. The most frequently reported infections included upper respiratory tract infection and nasopharyngitis. The common adverse event profile remained consistent during treatment period 2 and similar between subjects who underwent a single transition from EU-approved Enbrel to GP2015 and those who continued on EU-approved Enbrel.

Laboratory Abnormalities, Vital Signs and Electrocardiograms (ECGs)

No unexpected laboratory findings were reported in GP2015 clinical program.

Immunogenicity

An application submitted under section 351(k) of the PHS Act contains, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from "a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.[1] Immune responses against therapeutic biological products are a concern because they can negatively impact the drug's pharmacokinetics, safety, and efficacy. Unwanted immune reactions to therapeutic biological products are mostly caused by antibodies against the drug (anti-drug antibodies; ADA). Therefore, immunogenicity assessment for therapeutic biological products focuses on measuring ADA.

Immunogenicity Results from Studies in Healthy Subjects

Development of autoantibodies to the TNF-α receptor portion or other protein components of the US-licensed Enbrel drug product has been described in patients with RA, AS, PsA, and PsO. As described in the FDA-approved labeling for US-licensed Enbrel, the clinical significance of these autoantibodies is unknown. In the healthy subject studies, 101 and 102, all samples were negative for binding anti-etanercept antibodies (ADA). In study 104, three subjects who received GP2015 in period 1 and EU-approved Enbrel in period 2, had binding ADAs at the follow-up visit and a fourth subject had an indeterminate ADA result. The confirmed ADAs were below the lower limit of quantification and none of the ADAs were neutralizing.

[1] Section 351(k)(2)(A)(i)(I) of the PHS Act.

Immunogenicity Results from Study 302

In Study 302, immunogenicity data are available for all patients who were treated in treatment period 1 and treatment period 2. Binding ADAs were confirmed in 5 patients in the EU-approved Enbrel treatment arm as summarized in Table 24. None of these antibodies were neutralizing. No patients in the GP2015 treatment arm developed ADAs. In treatment period 2, no additional patients developed ADAs up to Week 30. There was no increase in ADA at Week 18 in those patients who transitioned study treatment as compared to those who continued on the treatment to which they were originally randomized.

Table 24. Anti-drug Antibody Response in Treatment Periods 1 and 2

Treatment Period 1	GP2015 N=264			EU-approved Enbrel N=267		
	Positive	Negative	Missing	Positive	Negative	Missing
Baseline	--	260	4	--	259	8
Week 2	--	250	14	1	253	13
Week 4	--	258	6	5	250	12
Week 8	--	251	13	--	248	19
Week 12	--	251	13	--	250	17

Treatment Period 2	Continued Original Treatment						Switched Treatments					
	Cont GP2015 N=150			Cont EU-Enbrel N=151			Switched EU-Enbrel N=96			Switched GP2015 N=100		
	Pos	Neg	Miss	Pos	Neg	Miss	Pos	Neg	Miss	Pos	Neg	Miss
Week 18	--	147	3	--	148	3	--	92	4	--	98	2
Week 30	--	140	10	--	141	10	--	91	5	--	95	5

Continued GP2015: GP2015 continued from Period 1
Continued Enbrel: EU-Enbrel continued from Period 2
Switched GP2015: Switched to treatment sequence EU-Enbrel>GP2015>EU-Enbrel in Period 2
Switched Enbrel: Switched to treatment sequence GP2015>EU-Enbrel>GP2015 in Period 2
Pos=Positive, Neg = Negative, Miss=Missing
Source: FDA analysis of data from Sandoz's 351(k) BLA submission

Based on the immunogenicity data from the single dose healthy subject studies, and the repeat dose study 302, there does not appear to be an increased risk of development of ADAs with treatment with GP2015 as compared to EU-approved Enbrel. Further, ADA formation did not increase following a single transition from EU-approved Enbrel to GP2015. Therefore, there are sufficient data supporting similar immunogenicity between GP2015, EU-approved Enbrel, and US-licensed Enbrel, and that immunogenicity adds to the totality of the evidence to support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel.

Overall Conclusion on Safety and Immunogenicity

The submitted safety and immunogenicity data and analyses are adequate to support the conclusion of no clinically meaningful differences between GP2015 and US-

approved Enbrel. The safety database submitted for GP2015 is adequate to provide a reasonable descriptive comparison between the two products. The analysis of the data indicates a safety profile similar to that of US-licensed Enbrel. There were no notable differences between GP2015 and EU-approved Enbrel in treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuations, and deaths between the treatment groups. No new safety signals have been identified compared to the known adverse event profile of US-licensed Enbrel. The FDA safety analysis is consistent with the Applicant's.

10 Considerations for Extrapolation of Biosimilarity

Sandoz seeks licensure for all indications for which US-licensed Enbrel is licensed (listed in Introduction section above). The GP2015 clinical program however, provides clinical efficacy and safety data from a clinical study in patients with PsO.

The Agency has determined that it may be appropriate for a biosimilar product to be licensed for one or more conditions of use (e.g., indications) for which the reference product is licensed, based on data from a clinical study(ies) performed in another condition of use. This concept is known as extrapolation. As described in the Guidance for Industry: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", if a biological product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for that product to be licensed for one or more additional conditions of use for which the reference product is licensed.[22] The Applicant needs to provide sufficient scientific justification for extrapolation, which should address, for example, the following issues for the tested and extrapolated conditions of use:

- The mechanism(s) of action (MOA), if known or can reasonably be determined, in each condition of use for which licensure is sought,
- The pharmacokinetics (PK) and bio-distribution of the product in different patient populations,
- The immunogenicity of the product in different patient populations,
- Differences in expected toxicities in each condition of use and patient population,
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought.

[22] Guidance for Industry "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", April 2015 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

As a scientific matter, the FDA has determined that differences between conditions of use with respect to the factors addressed in a scientific justification for extrapolation do not necessarily preclude extrapolation. Consistent with the principles outlined in the above FDA guidance, Sandoz has provided a justification for the proposed extrapolation of clinical data from studies in PsO to each of the other indications approved for US-licensed Enbrel for which Sandoz is seeking licensure, as summarized in this section.

First, Sandoz believes GP2015 is highly similar to US-licensed Enbrel based on extensive analytical characterization data, similar clinical pharmacokinetics, and similar efficacy, safety, and immunogenicity in an approved indication, as demonstrated in study GP15-302 in patients with plaque psoriasis.

Further, the additional points considered in the scientific justification for extrapolation of data to support biosimilarity in the indications for which Sandoz is seeking licensure (RA, JIA, PsA, and AS) include:

- The primary mode of action (MOA) of etanercept is through inhibiting binding of soluble TNF-α to cell-surface receptors and through binding transmembrane TNF-α, inhibiting subsequent signal transduction and adhesion molecule expression. The scientific literature indicates that this MOA is the primary MOA in RA, JIA, AS, PsA, and PsO. In contrast to monoclonal antibodies to TNF-α, complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity have not been considered to be clinically relevant mechanisms of etanercept. The data provided by Sandoz showed similar TNF-α binding and potency to neutralize TNFα, supporting the demonstration of analytical similarity pertinent to this MOA.

- The pharmacokinetic parameters of US-licensed Enbrel in patients with PsO were similar to those seen in patients with RA.[23] The estimated half-life of etanercept was about 100 hours and comparable in healthy subjects, JIA and RA patients. As a fusion glycoprotein and consisting entirely of human protein components, etanercept is expected to undergo proteolysis in patients across different diseases. There are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between GP2015 and US-licensed Enbrel in the indications sought for licensure. Since similar PK was demonstrated between GP2015 and US-licensed Enbrel in healthy subjects and psoriasis, a similar PK profile would be expected between GP2015 and US-licensed Enbrel in patients with RA, JIA, AS, and PsA.

- The immunogenicity of the US-licensed Enbrel was generally low (<10%).[23] In GP2015 clinical program, the ADA formation was also low and there were no notable differences between GP2015 and comparator Enbrel, both in patients

[23] FDA-approved Enbrel labeling

with plaque psoriasis, following repeat dosing without background immunosuppression, which is a reasonably sensitive setting, and in healthy subjects after single doses. Accordingly, similar immunogenicity would be expected between GP2015 and US-licensed Enbrel in patients with RA, JIA, PsA, and AS.

- Similar clinical safety profile with chronic dosing was demonstrated between GP2015 and EU-approved Enbrel in patients with plaque psoriasis, and following single doses in healthy subjects. As analytical and PK similarity was demonstrated between GP2015 and US-licensed Enbrel, a similar safety profile would be expected between GP2015 and US-licensed Enbrel in RA, JIA, PsA, and AS

In aggregate, the evidence indicates that the extrapolation of biosimilarity to the indications for which Sandoz is seeking licensure (RA, JIA, PsA, and AS) may be scientifically justified.

11 Summary

The conclusion of the comparison of the structural and functional properties of the clinical and commercial product lots of GP2015 and US-licensed Enbrel was that they were highly similar, notwithstanding minor differences in clinically inactive components.

Sandoz provided analytical and clinical pharmacology bridging data to scientifically justify the relevance of data obtained using EU-approved Enbrel to a demonstration of biosimilarity of GP2015 to the US-licensed Enbrel.

The submitted clinical pharmacology studies are adequate to (1) support the demonstration of PK similarity between GP2015 and US-licensed Enbrel, (2) establish the PK component of the scientific bridge to justify the relevance of the data generated using EU-approved Enbrel, and (3) justify the relevance of the PK findings from the GP2015 clinical program to the indications that were not directly studied in the GP2015 clinical program for which US-licensed Enbrel is licensed and for which Sandoz is seeking licensure.

The results of the clinical development program indicate that Sandoz's data would meet the requirement for a demonstration of "no clinically meaningful differences" between GP2015 and US-licensed Enbrel in terms of safety, purity, and potency in the indication studied. Specifically, the results from the comparative clinical efficacy, safety, and PK studies, which included chronic dosing regimens of GP2015 and EU-approved Enbrel in patients with PsO, and a single dose of 50 mg in healthy subjects of GP2015, EU-approved Enbrel, and US-licensed Enbrel, adequately supported the demonstration that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel in PsO. Further, the single transition from EU-approved Enbrel to GP2015 during the

second treatment period of GP15-302 in PsO patients did not result in different safety or immunogenicity profile. This would support the safety of a clinical scenario where non-treatment naïve patients undergo a single transition to GP2015.

In considering the totality of the evidence submitted, the data submitted by the Applicant show that GP2015 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel in terms of the safety, purity, and potency of the product.

The Applicant has also provided an extensive data package to address the scientific considerations for extrapolation of data to support biosimilarity to other conditions of use to support their request that GP2015 should receive licensure for each of the indications for which US-licensed Enbrel is currently licensed and for which GP2015 is seeking licensure.